

TITLE OF THE INVENTION
TYROSINE KINASE INHIBITORS

BACKGROUND OF THE INVENTION

5 Protein kinases (PKs) are enzymes that catalyze the phosphorylation of hydroxy groups on tyrosine, serine and threonine residues of proteins. The consequences of this seemingly simple activity are staggering; cell growth, differentiation and proliferation; i.e., virtually all aspects of cell life, in one way or another depend on PK activity. Furthermore, abnormal PK activity has been related to a host
10 of disorders, ranging from relatively non life-threatening diseases such as psoriasis to extremely virulent diseases such as glioblastoma (brain cancer). PKs can be broken into two classes, the protein tyrosine kinases (PTKs) and the serine-threonine kinases (STKs).

Certain growth factor receptors exhibiting PK activity are known as
15 receptor tyrosine kinases (RTKs). They comprise a large family of transmembrane receptors with diverse biological activity. As present, at least nineteen (19) distinct subfamilies of RTKs have been identified. One RTK subfamily contains the insulin receptor (IR), insulin-like growth factor I receptor (IGF-1R) and insulin receptor related receptor (IRR). IR and IGF-1R interact with insulin to activate a hetero-
20 tetramer composed of two entirely extracellular glycosylated α subunits and two β subunits which cross the cell membrane and which contain the tyrosine kinase domain. The Insulin-like Growth Factor-1 Receptor (IGF-1R), and its ligands, IGF-1 and IGF-2, are abnormally expressed in numerous tumors, including, but not limited to, breast, prostate, thyroid, lung, hepatoma, colon, brain, neuroendocrine, and others.

25 A more complete listing of the known RTK subfamilies is described in Plowman et al., KN&P, 1994, 7(6):334-339 which is incorporated by reference, including any drawings, as if fully set forth herein.

In addition to the RTKs, there also exists a family of entirely intracellular PTKs called "non-receptor tyrosine kinases" or "cellular tyrosine
30 kinases." This latter designation, abbreviated "CTK", will be used herein. CTKs do not contain extracellular and transmembrane domains. At present, over 24 CTKs in 11 subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes, Fps, Fak, Jak and Ack) have been identified. The Src subfamily appears so far to be the largest group of CTKs and includes Src, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk. For a more detailed

discussion of CTKs, see Bolen, *Oncogene*, 1993, 8:2025-2031, which is incorporated by reference, including any drawings, as if fully set forth herein.

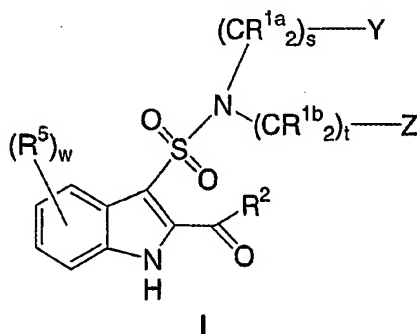
RTKs, CTKs and STKs have all been implicated in a host of pathogenic conditions including significantly, cancer. Other pathogenic conditions, which have been associated with PTKs include, without limitation, psoriasis, hepatic cirrhosis, diabetes, atherosclerosis, angiogenesis, restenosis, ocular diseases, rheumatoid arthritis and other inflammatory disorders, autoimmune diseases and a variety of renal disorders.

10 SUMMARY OF THE INVENTION

The present invention relates to compounds that are capable of inhibiting, modulating and/or regulating signal transduction of both receptor-type and non-receptor type tyrosine kinases. The compounds of the instant invention possess a core structure that comprises an indole-sulfonamide moiety. The present invention is also related to the pharmaceutically acceptable salts and stereoisomers of these compounds.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of kinases and are illustrated by a compound of Formula I:



wherein:

R^{1a} and R^{1b} are independently selected from:

- 1) hydrogen,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,

- 5
- 3) OR^3 ,
 - 4) $N(R^3)_2$,
 - 5) unsubstituted or substituted aryl,
 - 6) unsubstituted or substituted heterocycle, and
 - 7) unsubstituted or substituted C₃-C₁₀ cycloalkyl;

R^{1c} is independently selected from:

- 10
- 1) hydrogen,
 - 2) C₁-C₁₀ alkyl,
 - 3) OR^3 ,
 - 4) $N(R^3)_2$,
 - 5) C₃-C₁₀ cycloalkyl,
 - 6) aryl, and
 - 7) heterocycle;
- 15
- said alkyl, cycloalkyl, aryl and heterocycle is optionally substituted with at least one substituent selected from R⁷;

R² is independently selected from:

- 20
- 1) hydrogen,
 - 2) unsubstituted or substituted C₁-C₁₀ alkyl,
 - 3) $N(R^3)_2$,
 - 4) OR^3 ,
 - 5) unsubstituted or substituted aryl, and
 - 6) unsubstituted or substituted C₃-C₁₀ cycloalkyl;
- 25

R³ is independently selected from:

- 30
- 1) hydrogen,
 - 2) C₁-C₁₀ alkyl,
 - 3) aryl,
 - 4) heterocycle,
 - 5) C₃-C₁₀ cycloalkyl,
 - 6) CF₃,
 - 7) C₂-C₆ alkenyl,
 - 8) C₂-C₆ alkynyl,

9) $S(O)_mR^6$, and

10) $C(O)R^6$;

said alkyl, cycloalkyl, aryl, heterocycle, alkynyl, and alkenyl is optionally substituted with at least one substituent selected from R^7 ;

5

R^5 is independently selected from:

- 1) hydrogen,
- 2) halogen,
- 3) $-(CR^{1c_2})_nOR^3$,
- 10 4) $-(CR^{1c_2})_nR^6$,
- 5) $-C(O)OR^3$,
- 6) $-C(O)R^3$,
- 7) $-C\equiv CR^3$,
- 8) $-R^3C=C(R^3)_2$,
- 15 9) $-OS(O)_mR^6$,
- 10) $-NO_2$,
- 11) $-(CR^{1c_2})_nN(R^3)_2$,
- 12) $-N(R^3)C(O)R^3$,
- 13) $-N(R^3)S(O)_mR^6$,
- 20 14) $-(CR^{1c_2})_nNR^3(CR^{1c_2})_nC(O)NR^3_2$,
- 15) $-O(CR^{1c_2})_nC(O)N(R^3)_2$,
- 16) $-O(CR^{1c_2})_nC(O)OR^3$,
- 17) $-NR^3(CR^{1c_2})_nN(R^3)_2$,
- 18) $-(CR^{1c_2})_nNR^3R^6OR^3$,
- 25 19) $-S(O)_mR^6$,
- 20) $-S(O)_mN(R^3)_2$,
- 21) $-CN$,
- 22) $-(CR^{1c_2})_nN(R^3)(CR^{1c_2})_nR^6$, and
- 23) $-(CR^{1c_2})_nC(O)N(R^3)_2$;

30

R^6 is independently selected from:

- 1) C_1 - C_{10} alkyl,
- 2) C_3 - C_{10} cycloalkyl,
- 3) aryl, and

4) heterocycle;

said, alkyl, cycloalkyl, aryl and heterocycle is optionally substituted with at least one substituent selected from R⁷;

5 R⁷ is independently selected from:

- 1) hydrogen,
- 2) unsubstituted or substituted C₁-C₁₀ alkyl,
- 3) unsubstituted or substituted C₃-C₁₀ cycloalkyl,
- 4) unsubstituted or substituted aryl,
- 10 5) halogen,
- 6) OR³,
- 7) CF₃,
- 8) unsubstituted or substituted heterocycle,
- 9) S(O)_mN(R³)₂,
- 15 10) C(O)OR³,
- 11) C(O)R³,
- 12) CN,
- 13) C(O)N(R³)₂,
- 14) N(R³)C(O)R³,
- 20 15) S(O)_mR⁶, and
- 16) NO₂;

Y and Z are independently selected from:

- 1) hydrogen,
- 25 2) R⁶,
- 3) OR³,
- 4) N(R³)₂,
- 5) C(O)OR³,
- 6) C(O)N(R³)₂,
- 30 7) C(O)R³,
- 8) halogen,
- 9) N(R³)(CR^{1c2})_nC(O)N(R³)₂,
- 10) S(O)_mN(R³)₂,
- 11) N(R³)C(O)OR³,
- 35 12) N(R³)S(O)_mR⁶,

- 13) $N(R^3)C(O)R^3$,
 14) $N(R^3)(CR^{1c}_2)_nR^3$,
 15) $S(O)_mR^6$,
 16) $R^6S(O)_mN(R^3)_2$,
 5 17) $R^6S(O)_mR^6$,
 18) $N(R^3)S(O)_m(CR^{1c}_2)_nR^6$,
 19) $N(R^3)S(O)_mR^6OR^3$,
 20) $N(R^3)C(O)N(R^3)_2$,
 21) $N(R^3)C(O)R^6OR^3$,
 10 22) $N(R^3)(CR^{1c}_2)_nR^6OR^3$,
 23) $N(R^3)OR^3$, and
 24) $N(R^3)S(O)_mR^6NO_2$;

m is independently 0, 1 or 2;

15 n is independently 0 to 6;

s is 0 to 6;

t is 0 to 6;

w is 0 to 4;

20 or a pharmaceutically acceptable salt or stereoisomer thereof.

A second embodiment of the instant invention is a compound as illustrated above by Formula I wherein:

25 R^{1a} and R^{1b} are independently selected from:

- 1) hydrogen,
 2) unsubstituted or substituted C_1 - C_{10} alkyl,
 3) unsubstituted or substituted aryl,
 4) unsubstituted or substituted heterocycle, and
 30 5) OR^3 ;

R^{1c} is independently selected from:

- 1) hydrogen,
 2) C_1 - C_{10} alkyl,

- 3) OR^3 ,
- 4) $N(R^3)_2$,
- 5) aryl, and
- 6) heterocycle;

5 said alkyl, aryl and heterocycle is optionally substituted with at least one substituent selected from R^7 ;

R^2 is:

- 1) H,
- 10 2) unsubstituted or substituted alkyl,
- 3) OR^3 , or
- 4) $N(R^3)_2$;

R^3 is independently selected from:

- 15 1) hydrogen,
- 2) C_1 - C_{10} alkyl,
- 3) aryl,
- 4) heterocycle,
- 5) C_3 - C_{10} cycloalkyl,
- 20 6) CF_3 ,
- 7) $S(O)_mR^6$, and
- 8) $C(O)R^6$;

said alkyl, cycloalkyl, aryl and heterocycle is optionally substituted with at least one substituent selected from R^7 ;

25

R^5 is independently selected from:

- 1) hydrogen,
- 2) halogen,
- 3) $-OR^3$,
- 30 4) $-C(O)OR^3$,
- 5) $-C(O)R^3$,
- 6) $-C\equiv CR^3$,
- 7) $-R^3C=C(R^3)_2$,
- 8) $-OS(O)_mR^6$,

- 9) $-\text{NO}_2$,
 10) $-\text{N}(\text{R}^3)_2$,
 11) $-\text{N}(\text{R}^3)\text{C}(\text{O})\text{R}^3$,
 12) $-\text{N}(\text{R}^3)\text{S}(\text{O})_m\text{R}^6$,
 13) $-(\text{CR}^{1c}_2)_n\text{NR}^3(\text{CR}^{1c}_2)_nC(\text{O})\text{NR}^3_2$,
 14) $-\text{O}(\text{CR}^{1c}_2)_nC(\text{O})\text{N}(\text{R}^3)_2$,
 15) $-\text{O}(\text{CR}^{1c}_2)_nC(\text{O})\text{OR}^3$,
 16) $-\text{NR}^3(\text{CR}^{1c}_2)_n\text{N}(\text{R}^3)_2$,
 17) $-(\text{CR}^{1c}_2)_n\text{NR}^3\text{R}^6\text{OR}^3$,
 18) $-\text{S}(\text{O})_m\text{R}^6$,
 19) $-\text{S}(\text{O})_m\text{N}(\text{R}^3)_2$,
 20) $-\text{CN}$, and
 21) $-(\text{CR}^{1c}_2)_n\text{N}(\text{R}^3)(\text{CR}^{1c}_2)_n\text{R}^6$;

where n is 0 to 4;

and all other substituents and variables are as defined in the first embodiment;

or a pharmaceutically acceptable salt or stereoisomer thereof.

A further embodiment of the second embodiment is a compound as illustrated above by formula I wherein:

R^{1a} and R^{1b} are independently selected from hydrogen, unsubstituted or substituted $\text{C}_1\text{-C}_{10}$ alkyl, OR^3 , and unsubstituted or substituted aryl;

R^{1c} is independently selected from:

- 1) hydrogen,
 2) $\text{C}_1\text{-C}_{10}$ alkyl,
 3) OR^3 , and
 4) aryl;

said alkyl and aryl is optionally substituted with at least one substituent selected from R^7 ;

R² is:

- 1) OR³, or
- 2) N(R³)₂;

5 R⁵ is independently selected from:

- 1) hydrogen,
- 2) (CR^{1c2})_nR⁶,
- 3) halogen,
- 4) -(CR^{1c2})_nOR³,
- 10 5) -C(O)OR³,
- 6) -C(O)R³,
- 7) -C≡CR³,
- 8) -R³C=C(R³)₂,
- 9) (CR^{1c2})_nC(O)N(R³)₂, and
- 15 10) (CR^{1c2})_nN(R³)₂;

Y is:

- 1) hydrogen,
- 2) R⁶,
- 20 3) OR³,
- 4) C(O)R³,
- 5) C(O)N(R³)₂, or
- 6) N(R³)₂;

25 Z is:

- 1) hydrogen,
- 2) R⁶,
- 3) OR³,
- 4) N(R³)₂,
- 30 5) C(O)OR³,
- 6) C(O)N(R³)₂,
- 7) C(O)R³,
- 8) halogen,
- 9) N(R³)(CR^{1c2})_nC(O)N(R³)₂,

- 10) $S(O)_m N(R^3)_2$,
 11) $N(R^3)C(O)OR^3$,
 12) $N(R^3)S(O)_m R^6$,
 13) $N(R^3)C(O)R^3$,
 5 14) $N(R^3)(CR^{1c}_2)_n R^3$, or
 15) $S(O)_m R^6$;

n is independently 0 to 4;

- 10 and all other substituents and variables are as defined in the second embodiment;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Examples of compounds of the instant invention include

- 15 5-Chloro-3-[(methylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 3-(Aminosulfonyl)-5-chloro-1*H*-indole-2-carboxamide;
- 20 5-Bromo-3-({methyl[(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl] amino} sulfonyl)-1*H*-indole-2-carboxamide;
- 3-({[2-(Aminosulfonyl)ethyl]amino} sulfonyl)-5-iodo-1*H*-indole-2-carboxamide;
- 25 3-[(Dimethylamino)sulfonyl]-5-methoxy-1*H*-indole-2-carboxamide;
- 5-Chloro-3-{{[2-phenethyl]amino} sulfonyl}-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(benzylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 30 5-Chloro-3-[(cyclohexylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(1-naphthylamino)sulfonyl]-1*H*-indole-2-carboxamide;

- 5-Chloro-3-[(3-phenylpropyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(ethylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5 5-Chloro-3-[(propylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(butylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(pentylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 10 5-Chloro-3-{[ethyl(methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(diethylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 15 5-Chloro-3-[(*iso*-propylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(cyclobutylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(cyclopentylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 20 5-Chloro-3-[[4-chlorophenyl]amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[[3-chlorophenyl]amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 25 5-Chloro-3-[[2-chlorophenyl]amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[[4-chlorophenyl)methylamino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[[3-chlorophenyl)methylamino]sulfonyl]-1*H*-indole-2-carboxamide;
- 30 5-Chloro-3-[[2-chlorophenyl)methylamino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(*tert*-butylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 35 (±)-5-Chloro-3-[(pyrrolidin-3-ylamino)sulfonyl]-1*H*-indole-2-carboxamide;

- 5-Chloro-3-[(piperidin-4-ylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[[1-methyl-1*H*-benzimidazol-2-yl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5 5-Chloro-3-[(benzamideamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(5-aminotetrazole)sulfonyl]-1*H*-indole-2-carboxamide;
- 10 5-Chloro-3-[(pyridin-4-ylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(pyridin-2-ylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 15 5-Chloro-3-[(2-methoxyethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(dimethylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 3-([2-(Aminosulfonyl)ethyl]amino)sulfonyl]-5-chloro-1*H*-indole-2-carboxamide ;
- 20 5-Chloro-3-[(2-hydroxyethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Chloro-3-[(2-morpholin-4-ylethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 25 5-Chloro-3-[(2-methoxyethyl)(methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[[2-(2-acetamide)amino]ethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 30 *N*-{[2-(Aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl}-*N*-methyl-β-alaninamide;
- 5-Bromo-3-[(methylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- Ethyl *N*-{[2-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl} *N*-methyl-β-alaninate;
- 35

5-Bromo-3-{{cyclopropyl(methyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;

(±)-5-Bromo-3-{{methyl(tetrahydrofuran-3-yl)amino}sulfonyl}-1*H*-indole-2-carboxamide;

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5-Bromo-3-{{methyl[2-(1*H*-1,2,4-triazol-1-yl)ethyl]amino}sulfonyl}-1*H*-indole-2-carboxamide;

10 5-Bromo-3-{{methyl(tetrahydro-2*H*-pyran-4-yl)amino}sulfonyl}-1*H*-indole-2-carboxamide;

(±)-5-Bromo-3-{{[(1,4-dioxan-2-ylmethyl)(methyl)amino}sulfonyl]-1*H*-indole-2-carboxamide;

15 3-{{[4-(Aminosulfonyl)benzyl]amino}sulfonyl}-5-bromo-1*H*-indole-2-carboxamide;

5-Chloro-3-{{*iso*-propyl(2-methoxyethyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;

20 3-{{[(2-Bromoethyl)(2-hydroxyethyl)amino}sulfonyl]-5-hydroxy-1*H*-indole-2-carboxamide;

3-{{[(2-Bromoethyl)(2-hydroxyethyl)amino}sulfonyl]-5-methoxy-1*H*-indole-2-carboxamide;

25 5-Chloro-3-{{methoxy(methyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;

(±)-5-Chloro-3-{{[(2,3-dihydroxypropyl)(methyl)amino}sulfonyl]-1*H*-indole-2-carboxamide;

30 5-Chloro-3-{{[(2-hydroxyethyl)(methyl)amino}sulfonyl]-1*H*-indole-2-carboxamide;

N-{{[2-(Aminocarbonyl)-5-chloro-1*H*-indol-3-yl]sulfonyl}-*N*-methylglycine;

N-{{[2-(Aminocarbonyl)-5-chloro-1*H*-indol-3-yl]sulfonyl}-*N*-methylglycinamide;

35

- 5-Bromo-3-({[4-(methylsulfonyl)benzyl]amino}sulfonyl)-1*H*-indole-2-carboxamide;
- 3-[(2-[4-(Aminosulfonyl)phenyl]ethyl)amino]sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 5 3-[(5-Amino-5-oxopentyl)amino]sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 3-([2-(Aminosulfonyl)ethyl]amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 10 *tert*-Butyl 2-({[2-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl}amino)-ethylcarbamate;
- 3-[(2-Aminoethyl)amino]sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 15 5-Bromo-3-({[ethylsulfonylamino]ethylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Iodo-3-[(2-([4-methoxyphenyl]sulfonyl)amino)ethyl]amino]sulfonyl]-1 *H*-indole-2-carboxamide;
- 20 5-Bromo-3-([methoxy(methyl)amino]sulfonyl)-1*H*-indole-2-carboxamide;
- 5-Fluoro-3-[(2-([4-methoxyphenyl]sulfonyl)amino)ethyl](methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 25 5-Bromo-3-[(2-([4-nitrophenyl]sulfonyl)amino)ethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-([2-([4-methoxyphenyl]amino)carbonyl]amino)ethyl]amino]sulfonyl)-1*H*-indole-2-carboxamide;
- 30 5-Bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino]sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino]sulfonyl]-1 *H*-indole-2-carboxamide;
- 35

5-Bromo-3-[(3-[(4-chlorophenyl)sulfonyl]propyl)amino)sulfonyl]-1 *H*-indole-2-carboxamide;

5-Bromo-3-[(propylsulfonylamino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide
5 hydrochloride;

5-Bromo-3-[(2-[(4-methoxyphenyl)sulfonyl]amino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide ;

10 5-Bromo-3-[(2-[(phenylsulfonyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;

5-Bromo-3-[(2-[(methylsulfonyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;

15 3-[(2-[(Benzylsulfonyl)amino]ethyl)amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;

5-Bromo-3-[(2-[(3-methoxyphenyl)sulfonyl]amino)ethylamino)sulfonyl]-1*H*-
20 indole-2-carboxamide;

5-Bromo-3-[(2-[(2,5-dimethoxyphenyl)sulfonyl]amino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide;

25 5-Bromo-3-[(2-[(5-bromo-2-methoxyphenyl)sulfonyl]amino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide;

5-Bromo-3-[(2-[(2-(trifluoromethoxy)phenyl)sulfonyl]amino)ethylamino)sulfonyl]-1 *H*-indole-2-carboxamide;

30 5-Bromo-3-[(2-[(2-methoxy-5-methylphenyl)sulfonyl]amino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide;

5-Bromo-3-[(2-[(4-cyanophenyl)sulfonyl]amino)ethylamino)sulfonyl]-1*H*-indole-
35 2-carboxamide;

- 5-Bromo-3-[[2-[[4-chlorophenyl)sulfonyl]amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5 5-Bromo-3-[[2-[[3,4-dimethoxyphenyl)sulfonyl]amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[[3-[(phenylsulfonyl)amino]propyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 10 5-Bromo-3-[[3-[[4-methoxyphenyl)sulfonyl]amino]propyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 3-[[3-[(Benzylsulfonyl)amino]propyl]amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 15 3-[[2-[(Aminocarbonyl)amino]ethyl]amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 20 5-Bromo-3-[[2-[[4-bromophenyl)sulfonyl]amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[[2-[(thien-3-ylsulfonyl)amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 25 5-Bromo-3-[[2-[[3-chlorobenzyl)sulfonyl]amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[[2-[[2-phenylethyl)sulfonyl]amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 30 5-Bromo-3-[[2-[[4-methoxybenzoyl)amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide;

- 5-Bromo-3-[(2-[(4-methoxybenzyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[(2-[(4-methoxyphenyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[(2-[(4-methoxyphenyl)(methylsulfonyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 3-[(2-[Acetyl(4-methoxyphenyl)amino]ethyl)amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide;
- 5-Iodo-3-[(cyclopropyl(methyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Iodo-3-[(cyclopropylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Bromo-3-[(cyclopropylamino)sulfonyl]-1*H*-indole-2-carboxamide;
- 5-Iodo-3-[(methoxy(methyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- (±)-5-Chloro-3-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- (±)-5-Bromo-3-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- (±)-5-Iodo-3-[(tetrahydro-2*H*-pyran-2-ylmethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;
- (±)-5-Chloro-3-[(methyl(tetrahydro-2*H*-pyran-2-ylmethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide;

- (±)-5-Bromo-3-([methyl(tetrahydro-2H-pyran-2-ylmethyl)amino]sulfonyl)-1H-indole-2-carboxamide;
- (±)-5-Iodo-3-([methyl(tetrahydro-2H-pyran-2-ylmethyl)amino]sulfonyl)-1H-indole-2-carboxamide;
- 5 5-Bromo-3-([2-(tert-butylthio)ethyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 5-chloro-3-([methyl(tetrahydro-2H-pyran-4-yl)amino]sulfonyl)-1H-indole-2-carboxamide;
- 10 5-chloro-3-([1-(2,3-dihydro-1,4-benzodioxin-2-yl)ethyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 15 5-chloro-3-[(tetrahydro-2H-pyran-4-ylamino)sulfonyl]-1H-indole-2-carboxamide;
- 5-chloro-3-([(1,4-dioxan-2-ylmethyl)(methyl)amino]sulfonyl)-1H-indole-2-carboxamide;
- 20 5-chloro-3-([(3-methyloxetan-3-yl)methyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 5-chloro-3-[(tetrahydrofuran-3-ylamino)sulfonyl]-1H-indole-2-carboxamide;
- 5-chloro-3-([(1,1-dioxidotetrahydrothien-3-yl)methyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 25 5-chloro-3-([2-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 5-chloro-3-([2-(2-methoxyphenyl)ethyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 30 5-chloro-3-([3-(trifluoromethyl)benzyl]amino)sulfonyl)-1H-indole-2-carboxamide;
- 5-chloro-3-([2-(2,3-dihydro-1H-indol-1-yl)ethyl]amino)sulfonyl)-1H-indole-2-carboxamide;

- 5-chloro-3-({methyl[(1-methylpiperidin-3-yl)methyl]amino}sulfonyl)-1*H*-indole-2-carboxamide;
- 5 5-chloro-3-{{(2,3-dihydro-1,4-benzodioxin-2-ylmethyl) amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 5-bromo-3-{{(3-ethoxypropyl) amino}sulfonyl}-1*H*-indole-2-carboxamide;
3-{{{[2-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl}amino} methyl]-1-benzylpyrrolidine;
- 10 5-bromo-3-{{[(1-benzylpyrrolidin-3-yl)methyl]amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 15 5-bromo-3-{{(3-pyridin-3-ylpropyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 1-[2-{{{[2-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl}amino}ethyl]-4-phenylpiperidine;
- 20 5-bromo-3-{{(3-cyclohexylpropyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 5-bromo-3-{{(4,4-diphenylbutyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 5-bromo-3-{{(3-butoxypropyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 25 5-bromo-3-{{[(6,7,8,9-tetrahydro-5*H*-benzo[*a*][7]annulen-7-ylmethyl)amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 5-bromo-3-{{[3-(3,5-dimethyl-1*H*-pyrazol-1-yl)propyl]amino}sulfonyl}-1*H*-indole-2-carboxamide;
- 30 5-bromo-3-{{[3-(4-tert-butoxyphenyl)propyl]amino} sulfonyl}-1*H*-indole-2-carboxamide;

5-bromo-3-({[4-(4-tert-butoxyphenyl)butyl]amino}sulfonyl)-1H-indole-2-carboxamide;

5-bromo-3-({[2-methoxy-1-methylethyl]amino}sulfonyl)-1H-indole-2-carboxamide;

5

5-bromo-3-({[4-phenylbutyl]amino}sulfonyl)-1H-indole-2-carboxamide;

5-bromo-3-({[2-[(2,6-dichlorobenzyl)thio]ethyl]amino}sulfonyl)-1H-indole-2-carboxamide;

10

5-bromo-3-({[2-(tert-butylthio)ethyl]amino}sulfonyl)-1H-indole-2-carboxamide;

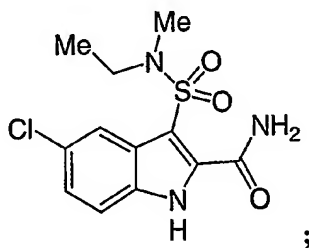
5-bromo-3-({[6-[(4-chlorobenzyl)amino]-6-oxohexyl]amino}sulfonyl)-1H-indole-2-carboxamide;

15

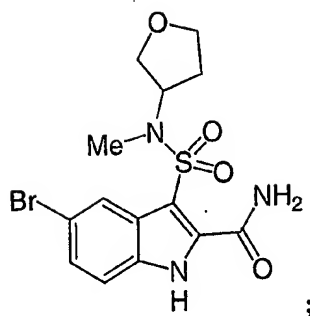
or the pharmaceutically acceptable salts or stereoisomers thereof.

Specific examples of compounds of the instant invention include

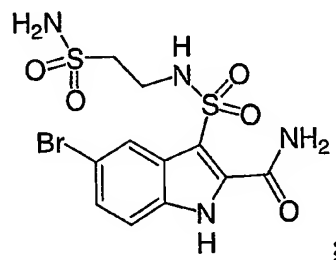
20 5-Chloro-3-({[ethyl(methyl)amino}sulfonyl]-1H-indole-2-carboxamide



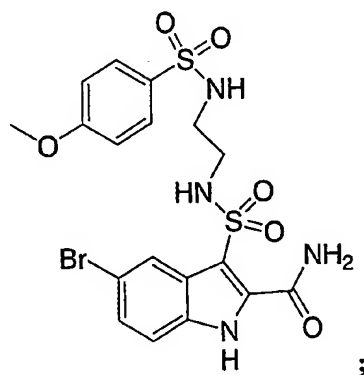
(±)-5-Bromo-3-({[methyl(tetrahydrofuran-3-yl)amino}sulfonyl]-1H-indole-2-carboxamide



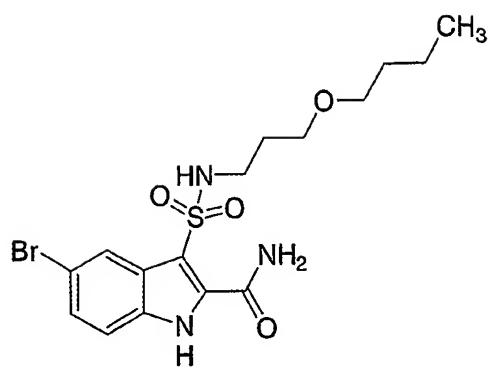
3-((2-(Aminosulfonyl)ethyl)amino)sulfonyl)-5-bromo-1*H*-indole-2-carboxamide



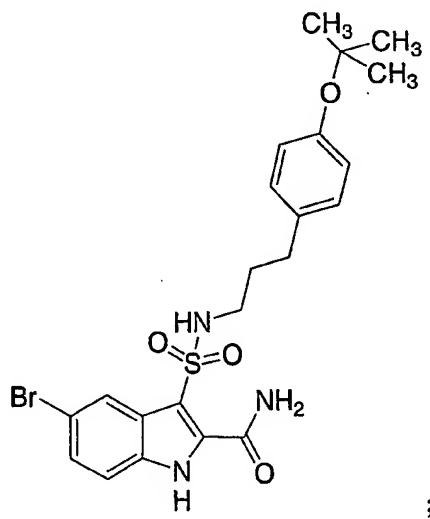
5-Bromo-3-(((2-((4-methoxyphenyl)sulfonyl)amino)ethyl)amino)sulfonyl)-1*H*-
5 indole-2-carboxamide



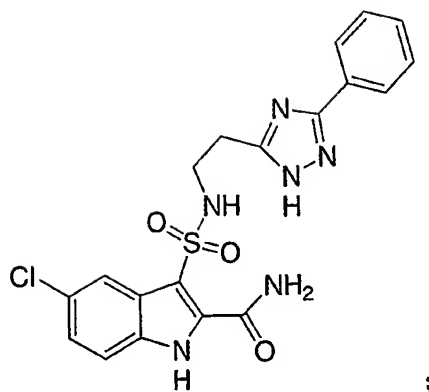
5-bromo-3-(((3-butoxypropyl)amino)sulfonyl)-1*H*-indole-2-carboxamide



5-bromo-3-((3-(4-tert-butoxyphenyl)propyl)amino)sulfonyl)-1H-indole-2-carboxamide



5 5-chloro-3-((2-(3-phenyl-1H-1,2,4-triazol-5-yl)ethyl)amino)sulfonyl)-1H-indole-2-carboxamide



or a pharmaceutically acceptable salt or stereoisomer thereof.

Also included in the instant invention is a process for preparing an
 5 alkyl 5-iodo-1*H*-indole-2-carboxylate which comprises the steps of:

- a) combining alkyl 1*H*-indole-2-carboxylate, iodine,
 sodium periodate and sulfuric acid in an alcohol, and
 heating to a temperature of about 50 °C to about 100 °C
 to obtain a product;
- 10 b) adding the product to a solution of organic solvent and
 aqueous solution to create a first biphasic mixture;
- c) extracting, drying, filtering and concentrating the
 organic layer;
- d) dissolving the organic layer in an alcohol;
- 15 e) adding zinc and aqueous acid to produce a mixture;
- f) combining the mixture with water to create a second
 biphasic mixture; and
- g) extracting, drying and filtering the organic layer of the
 second biphasic mixture to obtain the alkyl 5-iodo-1*H*-
 20 indole-2-carboxylate.

Preferably, the alkyl 5-iodo-1*H*-indole-2-carboxylate in the above
 process is ethyl 5-iodo-1*H*-indole-2-carboxylate.

25

The compounds of the present invention may have asymmetric centers, chiral axes, and chiral planes (as described in: E.L. Eliel and S.H. Wilen, Stereochemistry of Carbon Compounds, John Wiley & Sons, New York, 1994, pages 1119-1190), and occur as racemates, racemic mixtures, and as individual
5 diastereomers, with all possible isomers and mixtures thereof, including optical isomers, being included in the present invention. In addition, the compounds disclosed herein may exist as tautomers and both tautomeric forms are intended to be encompassed by the scope of the invention, even though only one tautomeric structure is depicted or named.

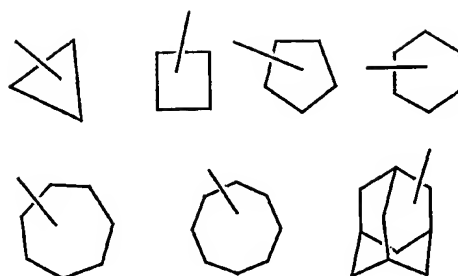
10 When any variable (e.g. R^{1b}, R³, aryl, heterocycle, n, etc.) occurs more than one time in any substituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents and variables are permissible only if such combinations result in stable compounds.

Lines drawn into the ring systems from substituents indicate that the
15 indicated bond may be attached to any of the substitutable ring carbon atoms or heteroatoms, including the carbon atom or heteroatom that is the point of attachment. If the ring system is polycyclic it is intended that the bond may be attached to any of the suitable carbon atoms or heteroatoms of any ring.

It is understood that substituents and substitution patterns on the
20 compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

As used herein, "alkyl" is intended to include both branched and
25 straight-chain aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C₁-C₁₀, as in "C₁-C₁₀ alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C₁-C₁₀ alkyl" specifically includes methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on.

30 "Cycloalkyl" as used herein is intended to include non-aromatic cyclic hydrocarbon groups, having the specified number of carbon atoms, which may or may not be bridged or structurally constrained. Examples of such cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, cycloheptyl, tetrahydro-naphthalene, methylenecyclohexyl, and the like. As
35 used herein, examples of "C₃ - C₁₀ cycloalkyl" may include, but are not limited to:



As used herein, the term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge.

If no number of carbon atoms is specified, the term "alkenyl" refers to
 5 a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to 4 non-aromatic carbon-carbon double bonds may be present. Thus, "C₂-C₆ alkenyl" means an alkenyl radical
 10 having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon
 15 triple bond. Up to 3 carbon-carbon triple bonds may be present. Thus, "C₂-C₆ alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

20 As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, indanonyl, indenyl, biphenyl, tetralinyl, tetralonyl, fluorenyl, phenanthryl, anthryl, acenaphthyl, tetrahydronaphthyl, and the like.

25 As appreciated by those of skill in the art, "halo" or "halogen" as used herein is intended to include chloro, fluoro, bromo and iodo.

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and

contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, indolyl, benzodioxolyl, benzotriazolyl, benzothiofuranyl, benzothiazolyl, furanyl, thienyl, benzothieryl,
5 benzofuranyl, benzoquinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrahydronaphthyl, tetrahydroquinoline, and the like.

The term heterocycle or heterocyclic or heterocyclyl, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic
10 heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.
15 "Heterocycle" or "heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzodioxolyl, benzofuranyl, benzofurazanyl, benzimidazolyl, benzopyranyl, benzopyrazolyl, benzotriazolyl, benzothiazolyl, benzothieryl, benzothiofuranyl, benzothiophenyl,
20 benzothiopyranyl, benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, diazapienyl, dihydrobenzodioxinyl, dihydrobenzofuranyl, dihydrobenzofuryl, dihydrobenzoimidazolyl, dihydrobenzothieryl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrocyclopentapyridinyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl,
25 dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothieryl, dihydrotriazolyl, dihydroazetidyl, dioxanyl, dioxidotetrahydrothieryl, furyl, furanyl, imidazolyl, imidazolinyl, imidazolidinyl,
30 imidazothiazolyl, imidazopyridinyl, indazolyl, indolazyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolyl, isoindolinyl, isoquinolinone, isoquinolyl, isothiazolyl, isothiazolidinyl, isoxazolyl, isoxazolyl, methylenedioxybenzoyl, morpholinyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazolinyl, oxetanyl, oxoazepinyl, oxadiazolyl, oxodihydrophthalazinyl, oxodihydroindolyl,
35 oxodihydrotriazolyl, oxoimidazolidinyl, oxopiperazinyl, oxopiperidinyl,

oxopyrrolidinyl, oxopyrimidinyl, oxopyrrolyl, oxotriazolyl, piperidyl, piperidinyl, piperazinyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinonyl, pyridopyridinyl, pyridazinyl, pyridyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolidinyl, quinazolinyl, quinolinyl, quinolyl, quinolinonyl, quinoxalyl, tetrahydrobenzoannulenyl, tetrahydrocycloheptapyridinyl, tetrahydrofuranlyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydropyranlyl, tetrahydroquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thiazolinyl, thienofuryl, thienyl, triazolyl, azetidyl, 1,4-dioxanyl, hexahydroazepinyl, and the like. Preferably, heterocycle is selected from oxoazepinyl, benzimidazolyl, dioxanyl, dihydrobenzodioxinyl, dihydroindolyl, Dihydrotriazolyl, dioxanyl, dioxidotetrahydrothienyl, oxetanyl, piperidinyl, pyrazolyl, pyridinyl, tetrahydrobenzoannulenyl, tetrahydrofuranlyl, tetrahydropyranlyl, tetrazolyl, imidazolyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, oxopiperidinyl, oxopyrrolidinyl, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, thienyl, and triazolyl.

As used herein, "aralkyl" is intended to mean an aryl moiety, as defined above, attached through a C₁-C₁₀ alkyl linker, where alkyl is defined above. Examples of aralkyls include, but are not limited to, benzyl, naphthylmethyl and phenylpropyl.

As used herein, "heterocyclalkyl" is intended to mean a heterocyclic moiety, as defined below, attached through a C₁-C₁₀ alkyl linker, where alkyl is defined above. Examples of heterocyclalkyls include, but are not limited to, pyridylmethyl, imidazolylethyl, pyrrolidinylmethyl, morpholinylethyl, quinolinylmethyl, imidazolylpropyl and the like.

As used herein, the terms "substituted C₁-C₁₀ alkyl" and "substituted C₁-C₆ alkoxy" are intended to include the branch or straight-chain alkyl group of the specified number of carbon atoms, wherein the carbon atoms may be substituted with 1 to 3 substituents selected from the group which includes, but is not limited to, halo, C₁-C₂₀ alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl) S(O)₀₋₂-, (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆ alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heterocycle, heterocyclalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclalkyl.

As used herein, the terms "substituted C₃-C₁₀ cycloalkyl", "substituted aryl", "substituted heterocycle", "substituted aralkyl" and "substituted heterocyclylalkyl" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound.

- 5 Preferably, the substituents are selected from the group which includes, but is not limited to, halo, C₁-C₂₀ alkyl, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, oxo, CN, N₃, -OH, -O(C₁-C₆ alkyl), C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, (C₀-C₆ alkyl)S(O)₀₋₂-, (C₀-C₆ alkyl)S(O)₀₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, -O(C₁-C₆ alkyl)CF₃, (C₀-C₆ alkyl)C(O)-, (C₀-C₆ alkyl)OC(O)-, (C₀-C₆ alkyl)O(C₁-C₆ alkyl)-, (C₀-C₆ alkyl)C(O)₁₋₂(C₀-C₆ alkyl)-, (C₀-C₆ alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocyclylalkyl, halo-aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

- 15 As used herein, the phrase "substituted with at least one substituent" is intended to mean that the substituted group being referenced has from 1 to 6 substituents. Preferably, the substituted group being referenced contains from 1 to 3 substituents, in addition to the point of attachment to the rest of the compound.

Preferably, R^{1a} and R^{1b} are independently selected from H, unsubstituted or substituted C₁-C₁₀ alkyl and OR³.

- 20 Preferably, R² is OR³ or N(R³)₂. Most preferably, R² is N(R³)₂.

Preferably R⁵ is independently selected from H, -(CR^{1c2})_nR⁶, halogen, -(CR^{1c2})_nOR³, and -(CR^{1c2})_nN(R³)₂. More preferably, R⁵ is independently selected from H, -(CR^{1c2})_nR⁶, halogen and -(CR^{1c2})_nOR³.

- 25 Preferably, Y is H, R⁶, OR³, N(R³)₂, or C(O)R³. More preferably, Y is H, R⁶ or OR³.

Preferably, w is 0, 1, 2 or 3. Most preferably, w is 0, 1, or 2.

Preferably, s and t are independently selected from 0, 1, 2, 3 and 4.

- 30 It is intended that the definition of any substituent or variable (e.g., R¹, R^{1a}, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R⁴)₂ represents -NHH, -NHCH₃, -NHC₂H₅, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by

techniques known in the art, as well as those methods set forth below, from readily available starting materials.

For use in medicine, the salts of the compounds of Formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N, N¹-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pantoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977:66:1-19.

It will also be noted that the compounds of the present invention are potentially internal salts or zwitterions, since under physiological conditions a deprotonated acidic moiety in the compound, such as a carboxyl group, may be anionic, and this electronic charge might then be balanced off internally against the

cationic charge of a protonated or alkylated basic moiety, such as a quaternary nitrogen atom.

Another embodiment of the instant invention is a process for preparing alkyl 5-iodo-1*H*-indole-2-carboxylate which comprises combining alkyl 1*H*-indole-2-carboxylate, iodine, sodium periodate and sulfuric acid in an alcohol and heated. Most preferably, the alkyl 5-iodo-1*H*-indole-2-carboxylate used is ethyl 5-iodo-1*H*-indole-2-carboxylate. Examples of alcohols that may be utilized include, but are not limited to, methanol, ethanol, *n*-propanol, *i*-propanol, butanol, an alkoxyethanol and the like. Preferably, the solution is heated to a temperature of about 50 °C to about 100 °C. Most preferably, the solution is heated to a temperature of about 75°C to about 85°C.

Next the product is added to a solution of organic solvent and aqueous solution to create a first biphasic mixture. Types of organic solvents that may be employed include, but are not limited to, ethyl acetate, isopropyl acetate, diethyl ether, dichloromethane, chloroform and the like. Examples of aqueous solutions include, but are not limited to, saturated aqueous sodium sulfite, aqueous sodium chloride, saturated sodium bicarbonate, saturated ammonium chloride, saturated sodium thiosulfate and the like. The organic layer of the first biphasic mixture is then removed, dried, filtered and concentrated. This organic layer is then dissolved in an alcohol. Zinc and aqueous acid is then added to produce a mixture. Types of acids that may be used in the instant invention, include, but are not limited to, hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The mixture is combined with water to create a second biphasic mixture. The organic layer of the second biphasic mixture is extracted, dried and filtered to obtain the alkyl 5-iodo-1*H*-indole-2-carboxylate.

Abbreviations, which may be used in the description of the chemistry and in the Examples that follow, include:

Ac ₂ O	Acetic anhydride;
AcOH	Acetic acid;
AIBN	2,2'-Azobisisobutyronitrile;

	Ar	Aryl;
	BINAP	2,2'-Bis(diphenylphosphino)-1,1' binaphthyl;
	Bn	Benzyl;
	BOC/Boc	<i>tert</i> -Butoxycarbonyl;
5	BSA	Bovine Serum Albumin;
	CAN	Ceric Ammonia Nitrate;
	CBz	Carbobenzyloxy;
	CI	Chemical Ionization;
	DBAD	Di- <i>tert</i> -butyl azodicarboxylate;
10	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene;
	DCC	1,3 Dichlorohexylcarbodiimide;
	DCE	1,2-Dichloroethane;
	DCM	Dichloromethane;
	DIEA	<i>N,N</i> -Diisopropylethylamine;
15	DMAP	4-Dimethylaminopyridine;
	DME	1,2-Dimethoxyethane;
	DMF	<i>N,N</i> -Dimethylformamide;
	DMSO	Methyl sulfoxide;
	DPPA	Diphenylphosphoryl azide;
20	DTT	Dithiothreitol;
	EDC	1-(3-Dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
	EDTA	Ethylenediaminetetraacetic acid;
	ELSD	Evaporative Light Scattering Detector;
	ES	Electrospray;
25	ESI	Electrospray ionization;
	Et ₂ O	Diethyl ether;
	Et ₃ N	Triethylamine;
	EtOAc	Ethyl acetate;
	EtOH	Ethanol;
30	FAB	Fast atom bombardment;
	HEPES	4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid;
	HMPA	Hexamethylphosphoramide;
	HOAc	Acetic acid;
	HOBT	1-Hydroxybenzotriazole hydrate;
35	HOBT	3-Hydroxy-1,2,2-benzotriazin-4(3 <i>H</i>)-one;

	HPLC	High-performance liquid chromatography;
	HRMS	High Resolution Mass Spectroscopy;
	KOtBu	Potassium <i>tert</i> -butoxide;
	LAH	Lithium aluminum hydride;
5	LCMS	Liquid Chromatography Mass Spectroscopy;
	MCPBA	<i>m</i> -Chloroperoxybenzoic acid;
	Me	Methyl;
	MeOH	Methanol;
	Ms	Methanesulfonyl;
10	MS	Mass Spectroscopy;
	MsCl	Methanesulfonyl chloride;
	<i>n</i> -Bu	<i>n</i> -butyl;
	<i>n</i> -Bu ₃ P	Tri- <i>n</i> -butylphosphine;
	NaHMDS	Sodium bis(trimethylsilyl)amide;
15	NBS	<i>N</i> -Bromosuccinimide;
	NMM	<i>N</i> -methylmorpholine;
	NMR	Nuclear Magnetic Resonance;
	Pd(PPh ₃) ₄	Palladium tetrakis(triphenylphosphine);
	Pd ₂ (dba) ₃	Tris(dibenzylideneacetone)dipalladium (0)
20	Ph	Phenyl;
	PMSF	α -Toluenesulfonyl fluoride;
	PS-DCC	Polystyrene dicyclohexylcarbodiimide;
	PS-DMAP	Polystyrene dimethylaminopyridine;
	PS-NMM	Polystyrene <i>N</i> -methylmorpholine;
25	Py or pyr	Pyridine;
	PYBOP	Benzotriazol-1-yloxytripyrrolidinophosphonium
	(or PyBOP)	hexafluorophosphate;
	RPLC	Reverse Phase Liquid Chromatography;
	RT	Room Temperature;
30	SCX SPE	Strong Cation Exchange Solid Phase Extraction;
	<i>t</i> -Bu	<i>tert</i> -Butyl;
	TBAF	Tetrabutylammonium fluoride;
	TBSCl	<i>tert</i> -Butyldimethylsilyl chloride;
	TFA	Trifluoroacetic acid;
35	THF	Tetrahydrofuran;

TIPS	Triisopropylsilyl;
TMS	Tetramethylsilane; and
Tr	Trityl.

5

UTILITY

In another aspect, this present invention relates to a method of modulating the catalytic activity of PKs (protein kinases) in a mammal in need thereof comprising contacting the PK with a compound of Formula I.

10

As used herein, the term "modulation" or "modulating" refers to the alteration of the catalytic activity of receptor tyrosine kinases (RTKs), cellular tyrosine kinases (CTKs) and serine-threonine kinases (STKs). In particular, modulating refers to the activation of the catalytic activity of RTKs, CTKs and STKs, preferably the activation or inhibition of the catalytic activity of RTKs, CTKs and

15

STKs, depending on the concentration of the compound or salt to which the RTKs, CTKs or STKs is exposed or, more preferably, the inhibition of the catalytic activity of RTKs, CTKs and STKs.

20

The term "catalytic activity" as used herein refers to the rate of phosphorylation of tyrosine under the influence, direct or indirect, of RTKs and/or CTKs or the phosphorylation of serine and threonine under the influence, direct or indirect, of STKs.

25

The term "contacting" as used herein refers to bringing a compound of this invention and a target PK together in such a manner that the compound can affect the catalytic activity of the PK, either directly; i.e., by interacting with the kinase itself, or indirectly; i.e., by interacting with another molecule on which the catalytic activity of the kinase is dependent. Such "contacting" can be accomplished "*in vitro*," i.e., in a test tube, a petri dish or the like. In a test tube, contacting may involve only a compound and a PK of interest or it may involve whole cells. Cells may also be maintained or grown in cell culture dishes and contacted with a compound in that

30

environment. In this context, the ability of a particular compound to affect a PK related disorder; i.e., the IC₅₀ of the compound, defined below, can be determined before use of the compounds *in vivo* with more complex living organisms is attempted. For cells outside the organism, multiple methods exist, and are well known to those skilled in the art, to get the PKs in contact with the compounds

including, but not limited to, direct cell microinjection and numerous transmembrane carrier techniques.

The above-referenced PK is selected from the group comprising an RTK, a CTK or an STK in another aspect of this invention. Preferably, the PK is an
5 RTK.

Furthermore, it is an aspect of this invention that the receptor tyrosine kinase (RTK) whose catalytic activity is modulated by a compound of this invention is selected from the group comprising EGF, HER2, HER3, HER4, IR, IGF-1R, IRR, PDGFR α , PDGFR β , TrkA, TrkB, TrkC, HGF, CSF1R, C-Kit, C-fms, Flk-1R, Flk4,
10 KDR/Flk-1, Flt-1, FGFR-1R, FGFR-1R, FGFR-3R and FGFR-4R. Preferably, the RTK is preferably, the receptor protein kinase is selected from IR, IGF-1R, or IRR.

In addition, it is an aspect of this invention that the cellular tyrosine kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak,
15 Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk.

Another aspect of this invention is that the serine-threonine protein kinase whose catalytic activity is modulated by a compound of this invention is selected from the group consisting of CDK2 and Raf.

In another aspect, this invention relates to a method for treating or
20 preventing a PK-related disorder in a mammal in need of such treatment comprising administering to the mammal a therapeutically effective amount of one or more of the compounds described above.

As used herein, "PK-related disorder," "PK driven disorder," and "abnormal PK activity" all refer to a condition characterized by inappropriate (i.e.,
25 diminished or, more commonly, excessive) PK catalytic activity, where the particular PK can be an RTK, a CTK or an STK. Inappropriate catalytic activity can arise as the result of either: (1) PK expression in cells which normally do not express PKs; (2) increased PK expression leading to unwanted cell proliferation, differentiation and/or growth; or, (3) decreased PK expression leading to unwanted reductions in cell
30 proliferation, differentiation and/or growth. Excessive-activity of a PK refers to either amplification of the gene encoding a particular PK or its ligand, or production of a level of PK activity which can correlate with a cell proliferation, differentiation and/or growth disorder (that is, as the level of the PK increases, the severity of one or more symptoms of a cellular disorder increase as the level of the PK activity decreases).

"Treat," "treating" or "treatment" with regard to a PK-related disorder refers to alleviating or abrogating the cause and/or the effects of a PK-related disorder.

As used herein, the terms "prevent", "preventing" and "prevention" refer to a method for barring a mammal from acquiring a PK-related disorder in the
5 first place.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof is provided in
10 combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or
15 medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The term "treating cancer" or "treatment of cancer" refers to administration to a mammal afflicted with a cancerous condition and refers to an effect that alleviates the cancerous condition by killing the cancerous cells, but also to
20 an effect that results in the inhibition of growth and/or metastasis of the cancer.

The protein kinase-related disorder may be selected from the group comprising an RTK, a CTK or an STK-related disorder in a further aspect of this invention. Preferably, the protein kinase-related disorder is an RTK-related disorder.

In yet another aspect of this invention, the above referenced PK-related
25 disorder may be selected from the group consisting of an EGFR-related disorder, a PDGFR-related disorder, an IGFR-related disorder and a flk-related disorder.

The above referenced PK-related disorder may be a cancer selected from, but not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, glioblastoma, bladder cancer, breast cancer, colorectal cancer, chondrosarcoma,
30 cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung
35 cancer, thymoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect

of this invention. More preferably, the PK-related disorder is a cancer selected from brain cancer, breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung cancer, renal cell carcinoma or endometrial carcinoma.

5 Included within the scope of the present invention is a pharmaceutical composition, which is comprised of a compound of Formula I as described above and a pharmaceutically acceptable carrier. The present invention also encompasses a method of treating or preventing cancer in a mammal in need of such treatment which is comprised of administering to said mammal a therapeutically effective amount of a compound of Formula I. Types of cancers which may be treated using compounds of
10 Formula I include, but are not limited to, astrocytoma, basal or squamous cell carcinoma, brain cancer, glioblastoma, bladder cancer, breast cancer, colorectal cancer, chondrosarcoma, cervical cancer, adrenal cancer, choriocarcinoma, esophageal cancer, endometrial carcinoma, erythroleukemia, Ewing's sarcoma, gastrointestinal cancer, head and neck cancer, hepatoma, glioma, hepatocellular carcinoma, leukemia, leiomyoma, melanoma, non-small cell lung cancer, neural cancer, ovarian cancer,
15 pancreatic cancer, prostate cancer, renal cell carcinoma, rhabdomyosarcoma, small cell lung cancer, thymoma, thyroid cancer, testicular cancer and osteosarcoma in a further aspect of this invention. More preferably, the cancer being treated is selected from breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-
20 small cell lung cancer, renal cell carcinoma, or endometrial carcinoma.

The above-referenced PK-related disorder may be an IGFR-related disorder selected from diabetes, an autoimmune disorder, Alzheimer's and other cognitive disorders, a hyperproliferation disorder, aging, cancer, acromegaly, Crohn's disease, endometriosis, diabetic retinopathy, restenosis, fibrosis, psoriasis,
25 osteoarthritis, rheumatoid arthritis, an inflammatory disorder and angiogenesis in yet another aspect of this invention.

A method of treating or preventing retinal vascularization which is comprised of administering to a mammal in need of such treatment a therapeutically effective amount of compound of Formula I is also encompassed by the present
30 invention. Methods of treating or preventing ocular diseases, such as diabetic retinopathy and age-related macular degeneration, are also part of the invention. Also included within the scope of the present invention is a method of treating or preventing inflammatory diseases, such as rheumatoid arthritis, psoriasis, contact dermatitis and delayed hypersensitivity reactions, as well as treatment or prevention of
35 bone associated pathologies selected from osteosarcoma, osteoarthritis, and rickets.

Other disorders which might be treated with compounds of this invention include, without limitation, immunological and cardiovascular disorders such as atherosclerosis.

The invention also contemplates the use of the instantly claimed
5 compounds in combination with a second compound selected from the group consisting of:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 3) retinoid receptor modulator,
- 10 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 8) an HIV protease inhibitor,
- 15 9) a reverse transcriptase inhibitor, and
- 10) angiogenesis inhibitor.

A preferred angiogenesis inhibitor is selected from the group consisting of a tyrosine kinase inhibitor, an inhibitor of epidermal-derived growth factor, an inhibitor of fibroblast-derived growth factor, an inhibitor of platelet derived
20 growth factor, an MMP inhibitor, an integrin blocker, interferon- α , interleukin-12, pentosan polysulfate, a cyclooxygenase inhibitor, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl-fumagillol, thalidomide, angiostatin, troponin-1, and an antibody to VEGF. Preferred estrogen receptor modulators are tamoxifen and raloxifene.

25 Also included in the scope of the claims is a method of treating cancer, which comprises administering a therapeutically effective amount of a compound of Formula I in combination with a compound selected from the group consisting of:

- 1) an estrogen receptor modulator,
- 2) an androgen receptor modulator,
- 30 3) retinoid receptor modulator,
- 4) a cytotoxic agent,
- 5) an antiproliferative agent,
- 6) a prenyl-protein transferase inhibitor,
- 7) an HMG-CoA reductase inhibitor,
- 35 8) an HIV protease inhibitor,

- 9) a reverse transcriptase inhibitor, and
- 10) angiogenesis inhibitor.

And yet another embodiment is the method of treating cancer using the combination discussed above, in combination with radiation therapy.

5 And yet another embodiment of the invention is a method of treating cancer which comprises administering a therapeutically effective amount of a compound of Formula I in combination with paclitaxel or trastuzumab. The PKs whose catalytic activity is modulated by the compounds of this invention include protein tyrosine kinases of which there are two types, receptor tyrosine kinases
10 (RTKs) and cellular tyrosine kinases (CTKs), and serine-threonine kinases (STKs). RTK-mediated signal transduction, is initiated by extracellular interaction with a specific growth factor (ligand), followed by receptor dimerization (or conformational changes in the case of IR, IGF-1R or IRR), transient stimulation of the intrinsic protein tyrosine kinase activity, autophosphorylation and subsequent phosphorylation
15 of other substrate proteins. Binding sites are thereby created for intracellular signal transduction molecules and lead to the formation of complexes with a spectrum of cytoplasmic signaling molecules that facilitate the appropriate cellular response (e.g., cell division, metabolic effects on the extracellular microenvironment, etc.). See Schlessinger and Ullrich, 1992, Neuron 9:303-391.

20 It has been shown that tyrosine phosphorylation sites, on growth factor receptors, function as high-affinity binding sites for SH2 (src homology) domains of signaling molecules. Fantl et al., 1992, Cell 69:413-423; Songyang et al., 1994, Mol., Cell. Biol. 14:2777-2785; Songyang et al., 1993, Cell 72:767-778; and Koch et al., 1991, Science 252:668-678. Another signaling molecule domain, which interacts
25 with phosphorylated tyrosines, is termed a PTB domain. Blaikie et al., 1994, J. Biol. Chem. 269:32031-32034; Gustafson et al., 1995, Mol. Cell Biol., 15:2500-25008; Kavanaugh and Williams, 1994, Science 266:1862-1865. Several intracellular substrate proteins that associate with RTKs have been identified. They may be divided into two principal groups: (1) substrates which have a catalytic domain; and
30 (2) substrates which lack such domain, but which serve as adapters and associate with catalytically active molecules. Songyang et al., 1993, Cell 72:767-778. The specificity of the interactions between receptors and SH2 domains of their substrates is determined by the amino acid residues immediately surrounding the phosphorylated tyrosine residue. Differences in the binding affinities between SH2 or PTB domains
35 and the amino acid sequences surrounding the phosphotyrosine residues on particular

receptors are consistent with the observed differences in their substrate phosphorylation profiles. Songyang et al., 1993, Cell 72:767-778. These observations suggest that the function of each RTK is determined not only by its pattern of expression and ligand availability, but also by the array of downstream signal transduction pathways that are activated by a particular receptor. Thus, phosphorylation provides an important regulatory step, which determines the selectivity of signaling pathways recruited by specific growth factor receptors, as well as differentiation factor receptors.

STKs, being primarily cytosolic, affect the internal biochemistry of the cell, often as a down-stream response to a PTK event. STKs have been implicated in the signaling process which initiates DNA synthesis and subsequent mitosis leading to cell proliferation.

Thus, PK signal transduction results in, among other responses, cell proliferation, differentiation, growth, metabolism, and cellular mobility. Abnormal cell proliferation may result in a wide array of disorders and diseases, including the development of neoplasia such as carcinoma, sarcoma, glioblastoma and hemangioma, disorders such as leukemia, psoriasis, arteriosclerosis, arthritis and diabetic retinopathy and other disorders related to uncontrolled angiogenesis and/or vasculogenesis.

A precise understanding of the mechanism by which the compounds of this invention inhibit PKs is not required in order to practice the present invention. However, while not hereby being bound to any particular mechanism or theory, it is believed that the compounds interact with the amino acids in the catalytic region of PKs. PKs typically possess a bi-lobate structure wherein ATP appears to bind in the cleft between the two lobes in a region where the amino acids are conserved among PKs. Inhibitors of PKs are believed to bind by non-covalent interactions such as hydrogen bonding, van der Waals forces and ionic interactions in the same general region where the aforesaid ATP binds to the PKs. The compounds disclosed herein may have utility as *in vitro* assays for such proteins as well as exhibiting *in vivo* therapeutic effects through interaction with such proteins.

In another aspect, the protein kinase (PK), the catalytic activity of which is modulated by contact with a compound of this invention, is a protein tyrosine kinase (PTK), more particularly, a receptor protein tyrosine kinase (RTK). Among the RTKs whose catalytic activity can be modulated with a compound of this invention, or salt thereof, are, without limitation, EGF, HER2, HER3, HER4, IR, IGF-

1R, IRR, PDGFR α , PDGFR β , TrkA, TrkB, TrkC, HGF, CSFIR, C-Kit, C-fms, Flk-1R, Flk4, KDR/Flk-1, Flt-1, FGFR-1R, FGFR-2R, FGFR-3R and FGFR-4R. Most preferably, the RTK is selected from IGF-1R.

5 The protein tyrosine kinase whose catalytic activity is modulated by contact with a compound of this invention, or a salt or a prodrug thereof, can also be a non-receptor or cellular protein tyrosine kinase (CTK). Thus, the catalytic activity of CTKs such as, without limitation, Src, Frk, Btk, Csk, Abl, ZAP70, Fes, Fps, Fak, Jak, Ack, Yes, Fyn, Lyn, Lck, Blk, Hck, Fgr and Yrk, may be modulated by contact with a compound or salt of this invention.

10 Still another group of PKs which may have their catalytic activity modulated by contact with a compound of this invention are the serine-threonine protein kinases such as, without limitation, CDK2 and Raf.

 This invention is also directed to compounds that modulate PK signal transduction by affecting the enzymatic activity of RTKs, CTKs and/or STKs, thereby
15 interfering with the signals transduced by such proteins. More particularly, the present invention is directed to compounds which modulate RTK, CTK and/or STK mediated signal transduction pathways as a therapeutic approach to cure many kinds of solid tumors, including, but not limited to, carcinomas, sarcomas including Kaposi's sarcoma, erythroblastoma, glioblastoma, meningioma, astrocytoma,
20 melonoma and myoblastoma. Treatment or prevention of non-solid tumor cancers such as leukemia are also contemplated by this invention. Indications may include, but are not limited to brain cancers, bladder cancers, ovarian cancers, gastric cancers, pancreatic cancers, colon cancers, blood cancers, breast cancers, prostate cancers, renal cell carcinomas, lung cancer and bone cancers.

25 Further examples, without limitation, of the types of disorders related to inappropriate PK activity that the compounds described herein may be useful in preventing, treating and studying, are cell proliferative disorders, fibrotic disorders and metabolic disorders.

 As previously mentioned, the Insulin-like Growth Factor-1 Receptor
30 (IGF-1R) belongs to the family of transmembrane tyrosine kinase receptors such as platelet-derived growth factor receptor, the epidermal growth factor receptor, and the insulin receptor. There are two known ligands for the IGF-1R receptor. They are IGF-1 and IGF-2. As used herein, the term "IGF" refers to both IGF-1 and IGF-2. The insulin-like growth factor family of ligands, receptors and binding proteins is

reviewed in Krywicki and Yee, *Breast Cancer Research and Treatment*, 22:7-19, 1992.

IGF/IGF-1R driven disorders are characterized by inappropriate or over-activity of IGF/IGF-1R. Inappropriate IGF activity refers to either: (1) IGF or IGF-1R expression in cells which normally do not express IGF or IGF-1R; (2) increased IGF or IGF-1R expression leading to unwanted cell proliferation such as cancer; (3) increased IGF or IGF-1R activity leading to unwanted cell proliferation, such as cancer; and/or over-activity of IGF or IGF-1R. Over-activity of IGF or IGF-1R refers to either an amplification of the gene encoding IGF-1, IGF-2, IGF-1R or the production of a level of IGF activity which can be correlated with a cell proliferative disorder (i.e., as the level of IGF increases the severity of one or more of the symptoms of the cell proliferative disorder increases) the bioavailability of IGF-1 and IGF-2 can also be affected by the presence or absence of a set of IGF binding proteins (IGF BPs) of which there are six known. Over activity of IGF/IGF-1R can also result from a down regulation of IGF-2 which contains an IGF-2 binding domain, but no intracellular kinase domain. Examples of IGF/IGF-1R driven disorders include the various IGF/IGF-1R related human malignancies reviewed in Cullen, *et al.*, *Cancer Investigation*, 9(4):443-454, 1991, incorporated herein by reference in its entirety, including any drawings. IGF/IGF-1Rs clinical importance and role in regulating osteoblast function is reviewed in Schmid, *Journal of Internal Medicine*, 234:535-542, 1993.

Thus, IGF-1R activities include: (1) phosphorylation of IGF-1R protein; (2) phosphorylation of an IGF-1R protein substrate; (3) interaction with an IGF adapter protein; (4) IGF-1R protein surface expression. Additional IGF-1R protein activities can be identified using standard techniques. IGF-1R activity can be assayed by measuring one or more of the following activities: (1) phosphorylation of IGF-1R; (2) phosphorylation of an IGF-1R substrate; (3) activation of an IGF-1R adapter molecule; and (4) activation of downstream signaling molecules, and/or (5) increased cell division. These activities can be measured using techniques described below and known in the arts.

IGF-1R has been implicated as an absolute requirement for the establishment and maintenance of the transformed phenotype both *in vitro* and *in vivo* in several cell types (R. Baserga, *Cancer Research* 55:249-252, 1995). Herbimycin A has been said to inhibit the IGF-1R protein tyrosine kinase and cellular proliferation in human breast cancer cells (Sepp-Lorenzino, *et al.*, 1994, *J. Cell Biochem. Suppl.* 18b:

246). Experiments studying the role of IGF-1R in transformation have used antisense strategies, dominant negative mutants, and antibodies to the IGF-1R and have led to the suggestion that IGR-1R may be a preferred target for therapeutic interventions.

IGF-1R, in addition to being implicated in nutritional support and in
5 type-II diabetes, has also been associated with several types of cancers. For example, IGF-1 has been implicated as an autocrine growth stimulator for several tumor types, e.g. human breast cancer carcinoma cells (Arteago et al., J. Clin. Invest., 1989, 84:1418-1423) and small lung tumor cells (Macauley et al., Cancer Res., 1989, 50:2511-2517). In addition, IGF-1, while integrally involved in the normal growth
10 and differentiation of the nervous system, also appears to be an autocrine stimulator of human gliomas. Sandberg-Nordqvist et al., Cancer Res., 1993, 53:2475-2478.

An example of IGF-2's potential involvement in colorectal cancer may be found in the up-regulation of IGF-2 mRNA in colon tumors relative to normal color tissue. (Zhang et al., Science (1997) 276:1268-1272.) IGF-2 may also play a
15 role in hypoxia induced neovascularization of tumors. (Minet et al., Int. J. Mol. Med. (2000) 5:253-259.) IGF-2 may also play a role in tumorigenesis through activation of an insulin receptor isoform-A. IGF-2 activation of insulin receptor isoform-A activates cell survival signaling pathways in cells but its relative contribution to tumor cell growth and survival is unknown at this time. Insulin receptor isoform-A's kinase
20 domain is identical to the standard insulin receptor's. Scalia et al., 2001, J. Cell Biochem. 82:610-618.

The importance of IGF-1R and its ligands in cell types in culture (fibroblasts, epithelial cells, smooth muscle cells, T-lymphocytes, myeloid cells, chondrocytes and osteoblasts (the stem cells of the bone marrow)) is illustrated by the
25 ability of IGF-1 to stimulate cell growth and proliferation. Goldring and Goldring, Eukaryotic Gene Expression, 1991, 1:301-326. In a series of recent publications, Baserga and others suggests that IGF-1R plays a central role in the mechanism of transformation and, as such, could be a preferred target for therapeutic interventions for a broad spectrum of human malignancies. Baserga, Cancer Res., 1995, 55:249-
30 252; Baserga, Cell, 1994, 79:927-930; Coppola et al., Mol. Cell. Biol., 1994, 14:4588-4595; Baserga, Trends in Biotechnology, 1996, 14:150-152; H.M. Khandwala et al., Endocrine Reviews, 21:215-244, 2000. The predominant cancers that may be treated using a compound of the instant invention include, but are not limited to breast cancer, prostate cancer, colorectal cancer, small cell lung cancer, non-small cell lung
35 cancer, renal cell carcinoma, or endometrial carcinoma.

IGF-1 has also been associated with retinal neovascularization.

Proliferative diabetes retinopathy has been seen in some patients having high levels of IGF-1. (L.E. Smith et al., *Nature Medicine*, 1999, 5:1390-1395.)

Compounds of the instant invention may also be useful as anti-aging agents. It has been observed that there is a link between IGF signalling and aging. Experiments have shown that calorie-restricted mammals have low levels of insulin and IGF-1 and have a longer life span. Similar observations have been made for insects as well. (See C. Kenyon, *Cell*, 2001, 105:165-168; E. Strauss, *Science*, 2001, 292:41-43; K.D. Kimura et al., *Science* 1997, 277:942-946; M. Tatar et al., *Science*, 2001, 292:107-110).

STKs have been implicated in many types of cancer including, notably, breast cancer (Cance et al., *Int. J. Cancer*, 1993, 54:571-77).

The association between abnormal PK activity and disease is not restricted to cancer. For example, RTKs have been associated with diseases such as psoriasis, diabetes mellitus, endometriosis, angiogenesis, atheromatous plaque development, Alzheimer's disease, epidermal hyperproliferation, neurodegenerative diseases, age-related macular degeneration and hemangiomas. For example, EGFR has been indicated in corneal and dermal wound healing. Defects in Insulin-R and IGF-1R are indicated in type-II diabetes mellitus. A more complete correlation between specific RTKs and their therapeutic indications is set forth in Plowman et al., *DN&P*, 1994, 7:334-339.

As noted previously, not only RTKs but CTKs including, but not limited to, src, abl, fps, yes, fyn, lyn, lck, Zap70, blk, hck, fgr and yrk (reviewed by Bolen et al., *FASEB J.*, 1993, 6:3403-3409) are involved in the proliferative and metabolic signal transduction pathway and thus could be expected, and have been shown, to be involved in many PTK-mediated disorders to which the present invention is directed. For example, mutated src (v-src) has been shown to be an oncoprotein (pp60^{v-src}) in chicken. Moreover, its cellular homolog, the protooncogene pp60^{c-src} transmits oncogenic signals of many receptors. Over-expression of EGFR or HER2/neu in tumors leads to the constitutive activation of pp60^{c-src}, which is characteristic of malignant cells, but absent in normal cells. On the other hand, mice deficient in the expression of c-src exhibit an osteopetrotic phenotype, indicating a key participation of c-src in osteoclast function and a possible involvement in related disorders.

Similarly, Zap70 has been implicated in T-cell signaling which may relate to autoimmune disorders.

STKs have been associated with inflammation, autoimmune disease, immunoresponses, and hyperproliferation disorders such as restenosis, fibrosis, psoriasis, osteoarthritis and rheumatoid arthritis.

PKs have also been implicated in embryo implantation. Thus, the compounds of this invention may provide an effective method of preventing such embryo implantation and thereby be useful as birth control agents.

Finally, both RTKs and CTKs are currently suspected as being involved in hyperimmune disorders.

These and other aspects of the invention will be apparent from the teachings contained herein.

A method for identifying a chemical compound that modulates the catalytic activity of one or more of the above discussed protein kinases is another aspect of this invention. The method involved contacting cells expressing the desired protein kinase with a compound of this invention (or its salt or prodrug) and monitoring the cells for any effect that the compound has on them. The effect may be any observable, either to the naked eye or through the use of instrumentation, change or absence of change in a cell phenotype. The change or absence of change in the cell phenotype monitored may be, for example, without limitation, a change or absence of change in the catalytic activity of the protein kinase in the cells or a change or absence of change in the interaction of the protein kinase with a natural binding partner.

COMPOSITION

Pharmaceutical compositions of the above compounds are a further aspect of this invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and

pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's bloodstream by local bolus injection.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, or alginic acid; binding agents, for example starch, gelatin, polyvinyl-pyrrolidone or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to mask the unpleasant taste of the drug or delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a water soluble taste masking material such as hydroxypropyl-methylcellulose or hydroxypropyl-cellulose, or a time delay material such as ethyl cellulose, cellulose acetate butyrate may be employed.

The compounds of the instant invention may also be co-administered with other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, in the case of bone-related disorders, combinations that would be useful include those with antiresorptive bisphosphonates, such as alendronate and risedronate; integrin blockers (defined further below), such as $\alpha_v\beta_3$ antagonists; conjugated estrogens used in hormone replacement therapy, such as PREMPRO®, PREMARIN® and ENDOMETRION®; selective estrogen receptor modulators (SERMs), such as raloxifene, droloxifene, CP-336,156 (Pfizer) and lasofoxifene; cathepsin K inhibitors; and ATP proton pump inhibitors.

The instant compounds are also useful in combination with known anti-cancer agents. Such known anti-cancer agents include the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors. The instant compounds are particularly useful when coadministered with radiation therapy. The synergistic effects of inhibiting VEGF in combination with radiation therapy have been described in the art. (see WO 00/61186.)

10 “Estrogen receptor modulators” refers to compounds, which interfere or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl)-phenyl]-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

 “Androgen receptor modulators” refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5 α -reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

20 “Retinoid receptor modulators” refers to compounds, which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α -difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

25 “Cytotoxic agents” refer to compounds which cause cell death primarily by interfering directly with the cell's functioning or inhibit or interfere with cell myosis, including alkylating agents, tumor necrosis factors, intercalators, microtubulin inhibitors, and topoisomerase inhibitors.

30 Examples of cytotoxic agents include, but are not limited to, tirapazimine, sertenef, cachectin, ifosfamide, tasonermin, lonidamine, carboplatin, doxorubicin, altretamine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-

pyridine) platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro) platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, idarubicin, daunorubicin,
 5 bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO00/50032).

Examples of microtubulin inhibitors include paclitaxel, vindesine
 10 sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincal leukoblastine, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, and BMS188797.

Some examples of topoisomerase inhibitors are topotecan,
 15 hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropirazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan,
 20 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydroxy-3,5-dimethoxyphenyl]-
 25 5,5a,6,8,8a,9-hexahydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and
 30 dimesna.

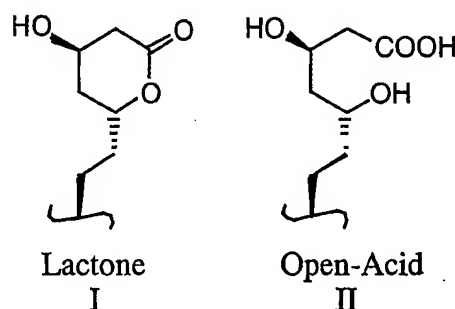
"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001,
 35 and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine,

trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea,
5 N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-mannoheptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-fluorouracil, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-
10 tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone. "Antiproliferative agents" also includes monoclonal antibodies to growth factors, other than those listed under "angiogenesis inhibitors", such as trastuzumab, and tumor suppressor genes,
15 such as p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Patent No. 6,069,134, for example).

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Compounds which have inhibitory activity for HMG-CoA reductase can be readily identified by using assays well-known in the art. For
20 example, see the assays described or cited in U.S. Patent 4,231,938 at col. 6, and WO 84/02131 at pp. 30-33. The terms "HMG-CoA reductase inhibitor" and "inhibitor of HMG-CoA reductase" have the same meaning when used herein.

Examples of HMG-CoA reductase inhibitors that may be used include, but are not limited to, lovastatin (MEVACOR[®], see U.S. Patent Nos. 4,231,938,
25 4,294,926 and 4,319,039); simvastatin (ZOCOR[®], see U.S. Patent Nos. 4,444,784, 4,820,850 and 4,916,239); pravastatin (PRAVACHOL[®], see U.S. Patent Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589); fluvastatin (LESCOL[®], see U.S. Patent Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896); atorvastatin (LIPITOR[®], see U.S. Patent Nos. 5,273,995,
30 4,681,893, 5,489,691 and 5,342,952); and cerivastatin (also known as rivastatin and BAYCHOL[®], see US Patent No. 5,177,080). The structural formulae of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314.
35 The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically

acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention. An illustration of the lactone portion and its corresponding open-acid form is shown below as structures I and II.



In HMG-CoA reductase inhibitors where an open-acid form can exist, salt and ester forms may preferably be formed from the open-acid, and all such forms are included within the meaning of the term "HMG-CoA reductase inhibitor" as used herein. Preferably, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin, and most preferably simvastatin. Herein, the term "pharmaceutically acceptable salts" with respect to the HMG-CoA reductase inhibitor shall mean non-toxic salts of the compounds employed in this invention which are generally prepared by reacting the free acid with a suitable organic or inorganic base, particularly those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc and tetramethylammonium, as well as those salts formed from amines such as ammonia, ethylenediamine, N-methylglucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, 1-p-chlorobenzyl-2-pyrrolidine-1'-yl-methylbenzimidazole, diethylamine, piperazine, and tris(hydroxymethyl)aminomethane. Further examples of salt forms of HMG-CoA reductase inhibitors may include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate,

lactobionate, laurate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate.

5 Ester derivatives of the described HMG-CoA reductase inhibitor compounds may act as prodrugs which, when absorbed into the bloodstream of a warm-blooded animal, may cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

“Prenyl-protein transferase inhibitor” refers to a compound which
 10 inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase). Examples of prenyl-protein transferase inhibiting compounds include (±)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-
 15 chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (-)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, (+)-6-[amino(4-chlorophenyl)(1-methyl-1H-imidazol-5-yl) methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone, 5(S)-n-butyl-1-(2,3-dimethylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, (S)-1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-5-[2-(ethanesulfonyl) methyl]-2-piperazinone,
 20 5(S)-n-Butyl-1-(2-methylphenyl)-4-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-2-piperazinone, 1-(3-chlorophenyl) -4-[1-(4-cyanobenzyl)-2-methyl-5-imidazolylmethyl]-2-piperazinone, 1-(2,2-diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoylethyl]piperidine, 4-{5-[4-hydroxymethyl-4-(4-chloropyridin-2-ylmethyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}
 25 benzonitrile, 4-{5-[4-hydroxymethyl-4-(3-chlorobenzyl)-piperidine-1-ylmethyl]-2-methylimidazol-1-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-pyridin-1-yl)benzyl]-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(5-chloro-2-oxo-2H-[1,2']bipyridin-5'-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 4-{3-[4-(2-oxo-2H-[1,2']bipyridin-5'-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 4-[3-(2-oxo-1-phenyl-1,2-dihydropyridin-4-ylmethyl)-3H-imidazol-4-ylmethyl}benzonitrile, 18,19-dihydro-19-oxo-5*H*,17*H*-6,10:12,16-dimetheno-1H-imidazo[4,3-*c*][1,11,4]dioxazacyclo -
 nonadecine-9-carbonitrile, (±)-19,20-dihydro-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo[*d*]imidazo[4,3-*k*][1,6,9,12]oxatriaza-cyclooctadecine-9-
 30 carbonitrile, 19,20-dihydro-19-oxo-5*H*,17*H*-18,21-ethano-6,10:12,16-dimetheno-22*H*-

imidazo[3,4-*h*][1,8,11,14]oxatriazacycloeicosine-9-carbonitrile, and (±)-19,20-dihydro-3-methyl-19-oxo-5*H*-18,21-ethano-12,14-etheno-6,10-metheno-22*H*-benzo [*d*]imidazo[4,3-*k*][1,6,9,12]oxa-triazacyclooctadecine-9-carbonitrile.

Other examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Patent No. 5,420,245, U.S. Patent No. 5,523,430, U.S. Patent No. 5,532,359, U.S. Patent No. 5,510,510, U.S. Patent No. 5,589,485, U.S. Patent No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Patent No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Patent No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Patent No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see European J. of Cancer, Vol. 35, No. 9, pp.1394-1401 (1999).

Examples of HIV protease inhibitors include amprenavir, abacavir, CGP-73547, CGP-61755, DMP-450, indinavir, nelfinavir, tipranavir, ritonavir, saquinavir, ABT-378, AG 1776, and BMS-232,632. Examples of reverse transcriptase inhibitors include delaviridine, efavirenz, GS-840, HB Y097, lamivudine, nevirapine, AZT, 3TC, ddC, and ddI.

“Angiogenesis inhibitors” refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to, tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR20), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon- α , interleukin-12, pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-

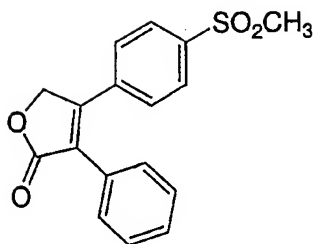
genase-2 inhibitors like celecoxib and rofecoxib (PNAS, Vol. 89, p. 7384 (1992); JNCI, Vol. 69, p. 475 (1982); Arch. Ophthalmol., Vol. 108, p.573 (1990); Anat. Rec., Vol. 238, p. 68 (1994); FEBS Letters, Vol. 372, p. 83 (1995); Clin. Orthop. Vol. 313, p. 76 (1995); J. Mol. Endocrinol., Vol. 16, p.107 (1996); Jpn. J. Pharmacol., Vol. 75, 5 p. 105 (1997); Cancer Res., Vol. 57, p. 1625 (1997); Cell, Vol. 93, p. 705 (1998); Intl. J. Mol. Med., Vol. 2, p. 715 (1998); J. Biol. Chem., Vol. 274, p. 9116 (1999)), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez *et al.*, J. Lab. Clin. Med. 105:141-145 (1985)), and antibodies to VEGF. 10 (see, Nature Biotechnology, Vol. 17, pp.963-968 (October 1999); Kim *et al.*, Nature, 362, 841-844 (1993); WO 00/44777; and WO 00/61186).

As described above, the combinations with NSAID's are directed to the use of NSAID's which are potent COX-2 inhibiting agents. For purposes of this specification an NSAID is potent if it possess an IC₅₀ for the inhibition of COX-2 of 15 1μM or less as measured by the cell or microsomal assay disclosed herein.

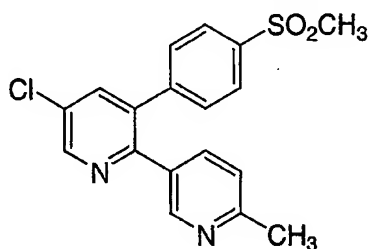
The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC₅₀ 20 for COX-2 over IC₅₀ for COX-1 evaluated by the cell or microsomal assay disclosed hereinunder. Such compounds include, but are not limited to those disclosed in U.S. 5,474,995, issued December 12, 1995, U.S. 5,861,419, issued January 19, 1999, U.S. 6,001,843, issued December 14, 1999, U.S. 6,020,343, issued February 1, 2000, U.S. 5,409,944, issued April 25, 1995, U.S. 5,436,265, issued July 25, 1995, U.S. 25 5,536,752, issued July 16, 1996, U.S. 5,550,142, issued August 27, 1996, U.S. 5,604,260, issued February 18, 1997, U.S. 5,698,584, issued December 16, 1997, U.S. 5,710,140, issued January 20, 1998, WO 94/15932, published July 21, 1994, U.S. 5,344,991, issued June 6, 1994, U.S. 5,134,142, issued July 28, 1992, U.S. 5,380,738, issued January 10, 1995, U.S. 5,393,790, issued February 20, 1995, U.S. 5,466,823, 30 issued November 14, 1995, U.S. 5,633,272, issued May 27, 1997, and U.S. 5,932,598, issued August 3, 1999, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are:

3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(5H)-furanone; and



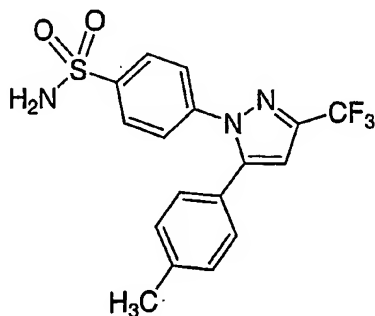
5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine;

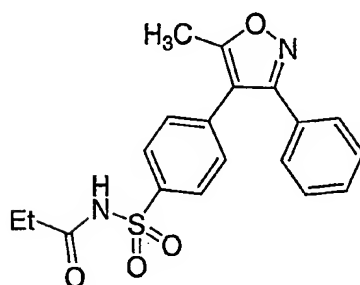
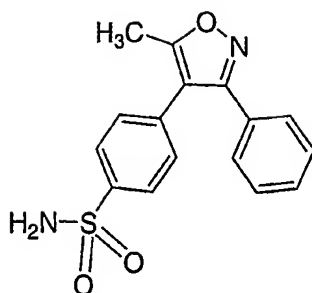


or a pharmaceutically acceptable salt thereof.

5 General and specific synthetic procedures for the preparation of the COX-2 inhibitor compounds described above are found in U.S. Patent No. 5,474,995, issued December 12, 1995, U.S. Patent No. 5,861,419, issued January 19, 1999, and U.S. Patent No. 6,001,843, issued December 14, 1999, all of which are herein incorporated by reference.

10 Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to, the following:





or a pharmaceutically acceptable salt thereof.

Compounds, which are described as specific inhibitors of COX-2 and
5 are therefore useful in the present invention, and methods of synthesis thereof, can be found in the following patents, pending applications and publications, which are herein incorporated by reference: WO 94/15932, published July 21, 1994, U.S. Patent No. 5,344,991, issued June 6, 1994, U.S. Patent No. 5,134,142, issued July 28, 1992, U.S. Patent No. 5,380,738, issued January 10, 1995, U.S. Patent No. 5,393,790,
10 issued February 20, 1995, U.S. Patent No. 5,466,823, issued November 14, 1995, U.S. Patent No. 5,633,272, issued May 27, 1997, and U.S. Patent No. 5,932,598, issued August 3, 1999.

Compounds which are specific inhibitors of COX-2 and are therefore
useful in the present invention, and methods of synthesis thereof, can be found in the
15 following patents, pending applications and publications, which are herein incorporated by reference: U.S. Patent No. 5,474,995 issued December 12, 1995, U.S. Patent No. 5,861,419 issued January 19, 1999, U.S. Patent No. 6,001,843 issued December 14, 1999, U.S. Patent No. 6,020,343 issued February 1, 2000, U.S. Patent No. 5,409,944 issued April 25, 1995, U.S. Patent No. 5,436,265 issued July 25, 1995,
20 U.S. Patent No. 5,536,752 issued July 16, 1996, U.S. Patent No. 5,550,142 issued August 27, 1996, U.S. Patent No. 5,604,260 issued February 18, 1997, U.S. Patent

No. 5,698,584 issued December 16, 1997, and U.S. Patent No. 5,710,140 issued January 20, 1998.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide, CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonyl-imino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counter-act binding of a physiological ligand to the $\alpha_v\beta_5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl]indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, STI571, CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

The instant compounds are also useful, alone or in combination with platelet fibrinogen receptor (GP IIb/IIIa) antagonists, such as tirofiban, to inhibit metastasis of cancerous cells. Tumor cells can activate platelets largely via thrombin

generation. This activation is associated with the release of VEGF. The release of VEGF enhances metastasis by increasing extravasation at points of adhesion to vascular endothelium (Amirkhosravi, *Platelets* 10, 285-292, 1999). Therefore, the present compounds can serve to inhibit metastasis, alone or in combination with GP
5 IIb/IIIa) antagonists. Examples of other fibrinogen receptor antagonists include abciximab, eptifibatide, sibrafiban, lamifiban, lotrafiban, cromofiban, and CT50352.

FORMULATIONS

The compounds of this invention may be administered to mammals,
10 preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers, excipients or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and/or topical routes
15 of administration.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent(s) within its approved dosage range. Compounds of the instant invention may alternatively be used sequentially with known pharmaceutically
20 acceptable agent(s) when a combination formulation is inappropriate.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water soluble carrier such as
25 polyethyleneglycol or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

For oral use of a compound according to this invention, particularly for chemotherapy, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets
30 for oral use, carriers which are commonly used include lactose and cornstarch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or
35 flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and

intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

5 Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring
10 phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylene-oxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or
15 condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

20 Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a
25 palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as butylated hydroxyanisol or alpha-tocopherol.

 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more
30 preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

 The pharmaceutical compositions of the invention may also be in the
35 form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for

example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example soy bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and
5 condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring agents, preservatives and antioxidants.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also
10 contain a demulcent, a preservative, flavoring and coloring agents and antioxidant.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous solution. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution.

The sterile injectable preparation may also be a sterile injectable oil-in-
15 water microemulsion where the active ingredient is dissolved in the oily phase. For example, the active ingredient may be first dissolved in a mixture of soybean oil and lecithin. The oil solution then introduced into a water and glycerol mixture and processed to form a microemulsion.

The injectable solutions or microemulsions may be introduced into a
20 patient's bloodstream by local bolus injection. Alternatively, it may be advantageous to administer the solution or microemulsion in such a way as to maintain a constant circulating concentration of the instant compound. In order to maintain such a constant concentration, a continuous intravenous delivery device may be utilized. An example of such a device is the Deltec CADD-PLUS™ model 5400 intravenous
25 pump.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension for intramuscular and subcutaneous administration. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents, which have been
30 mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In
35 addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of Formula I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter, glycerinated
5 gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.)
10

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles and delivery devices, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal
15 delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

20 Additionally, the compounds of the instant invention may be administered to a mammal in need thereof using a gel extrusion mechanism (GEM) device, such as that described in U.S. Patent No. 4,976,697, filed on December 11, 1990, which is hereby incorporated by reference.

When a compound according to this invention is administered into a
25 human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

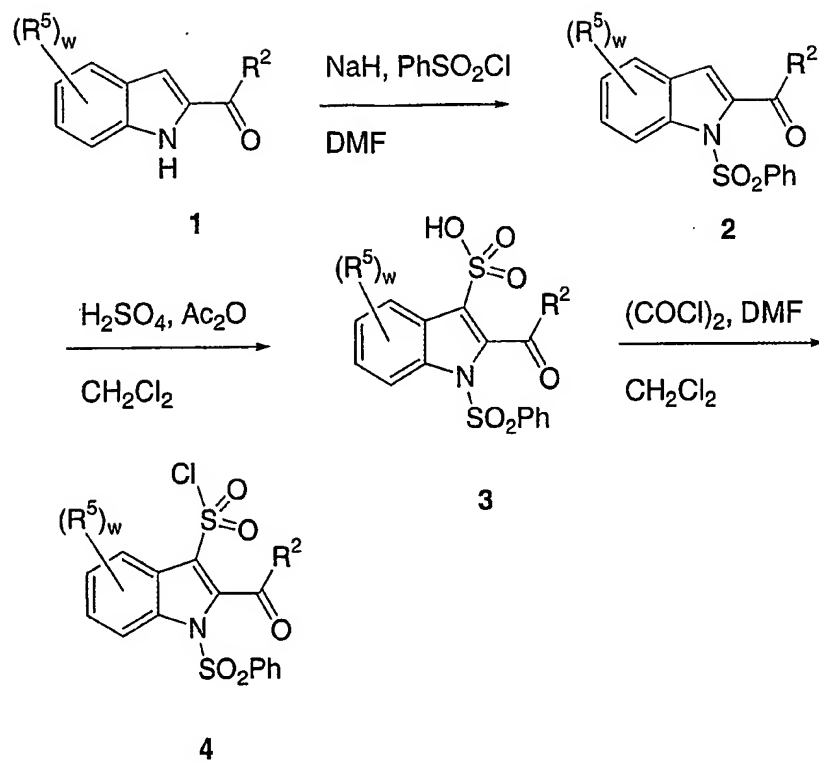
In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in
30 an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

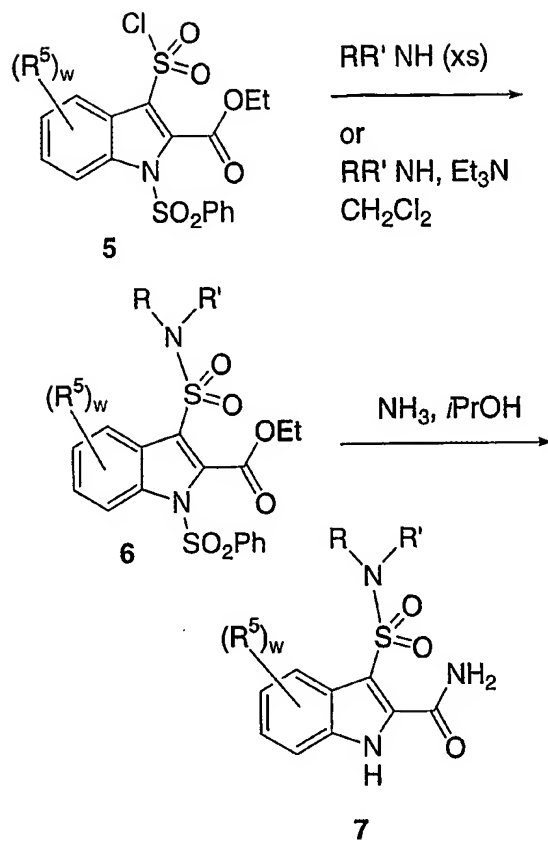
The compounds of this invention may be prepared by employing reactions as shown in the following schemes, in addition to other standard
35 manipulations that are known in the literature or exemplified in the experimental

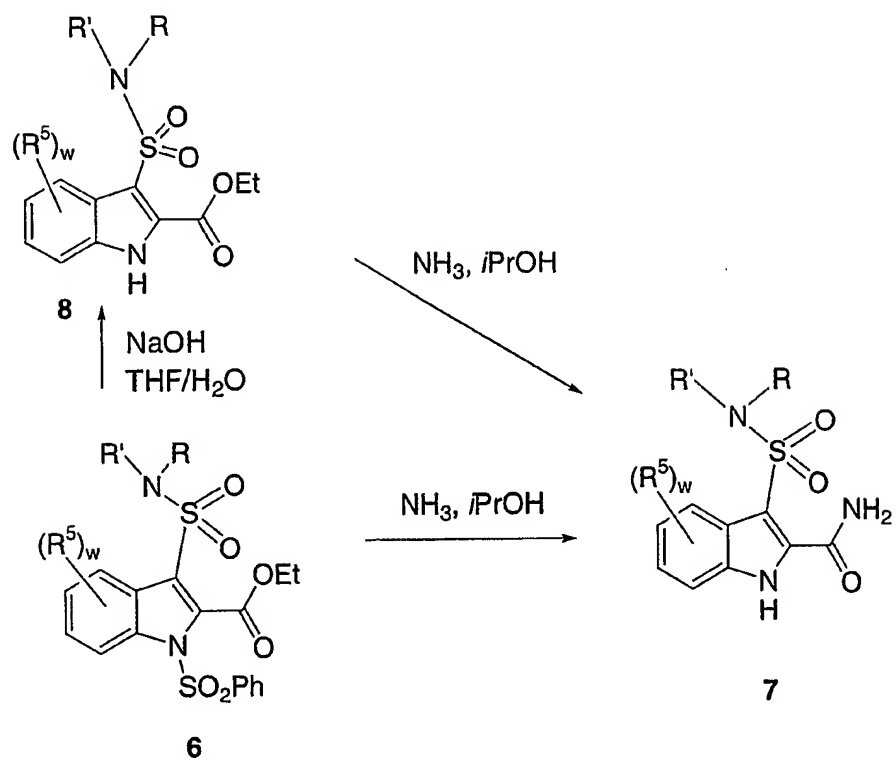
procedures. These schemes, therefore, are not limited by the compounds listed, nor by any particular substituents employed for illustrative purposes. Substituent numbering, as shown in the schemes, does not necessarily correlate to that used in the claims. In Schemes 1-15, R represents $-(CR^{1a}_2)_s-Y$, and R' represents $-(CR^{1b}_2)_t-$

5 Z.

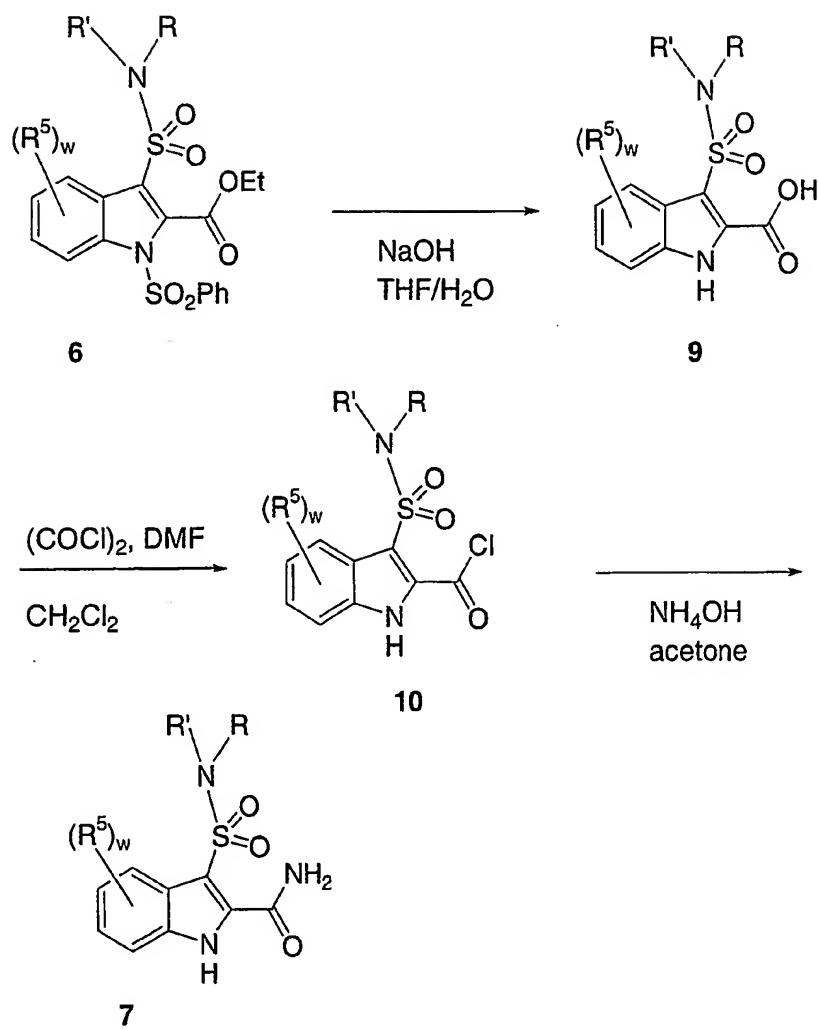
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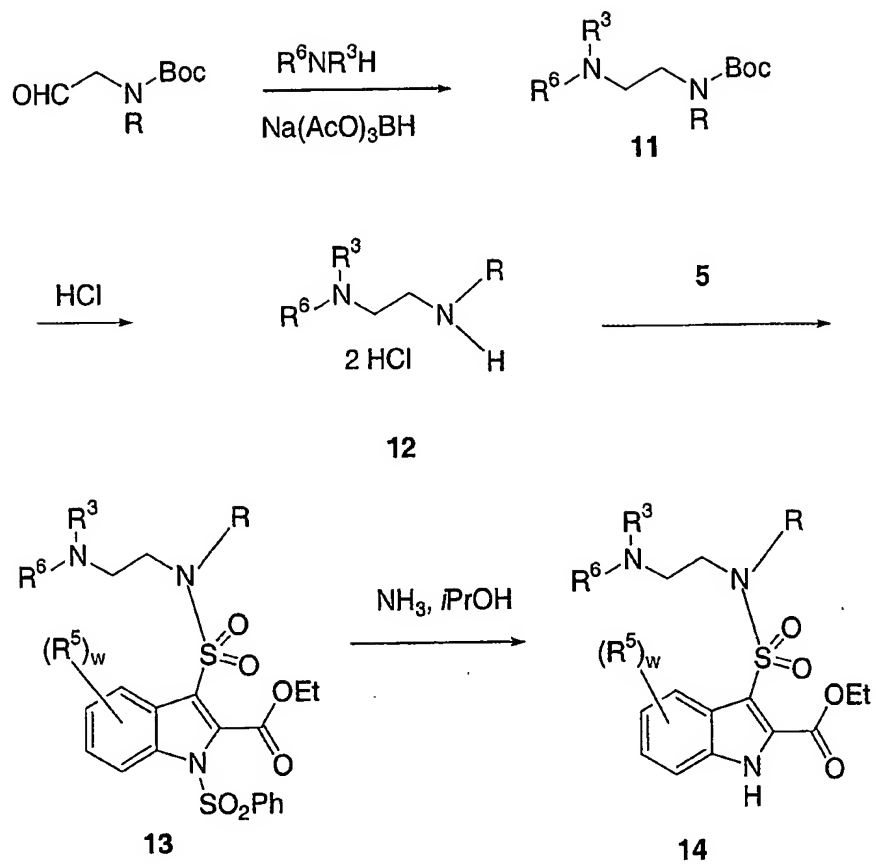
SCHEME 2

SCHEME 3

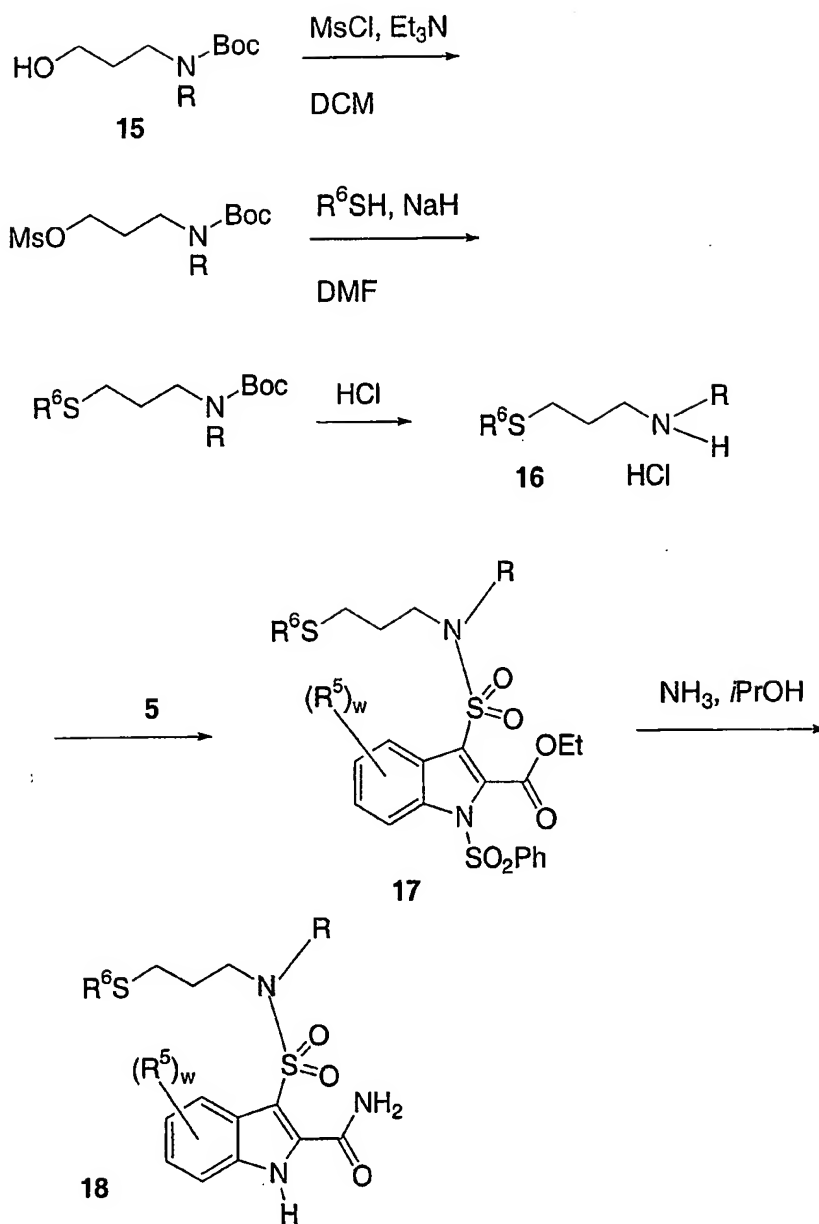
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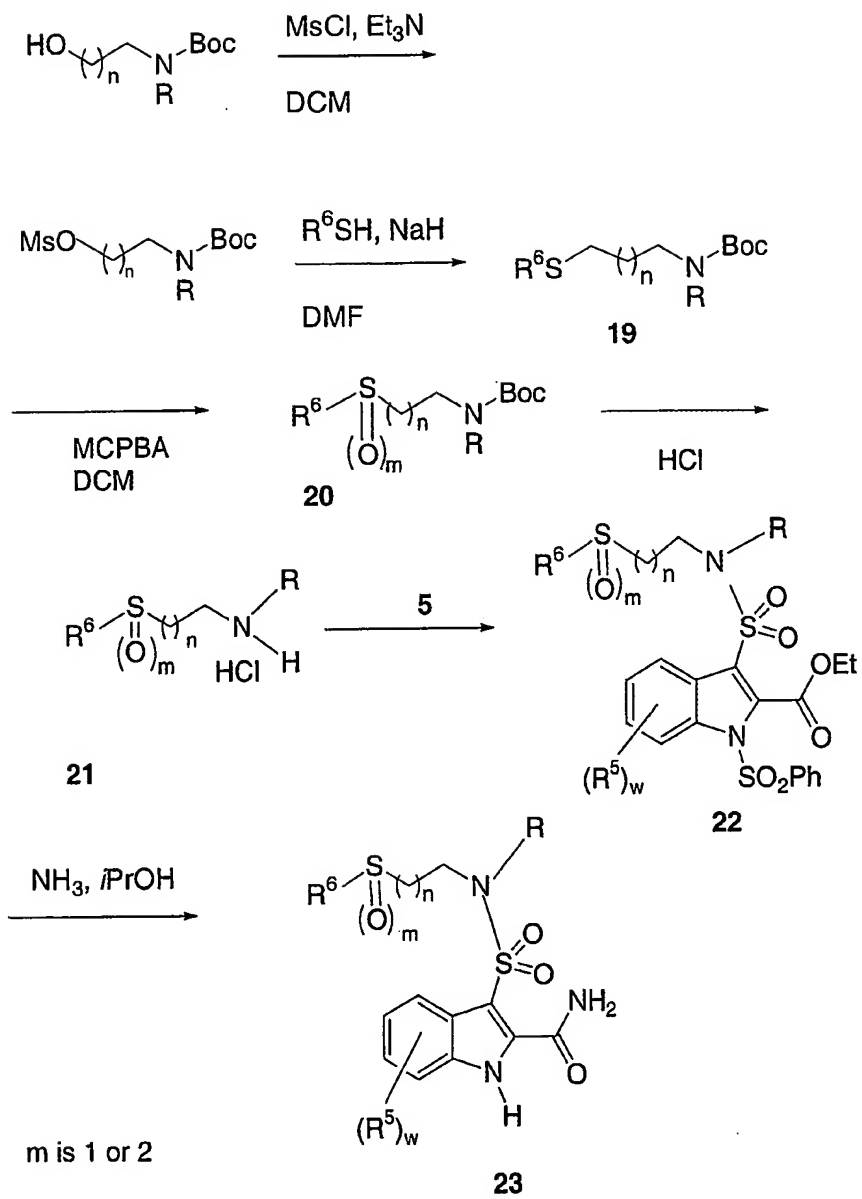
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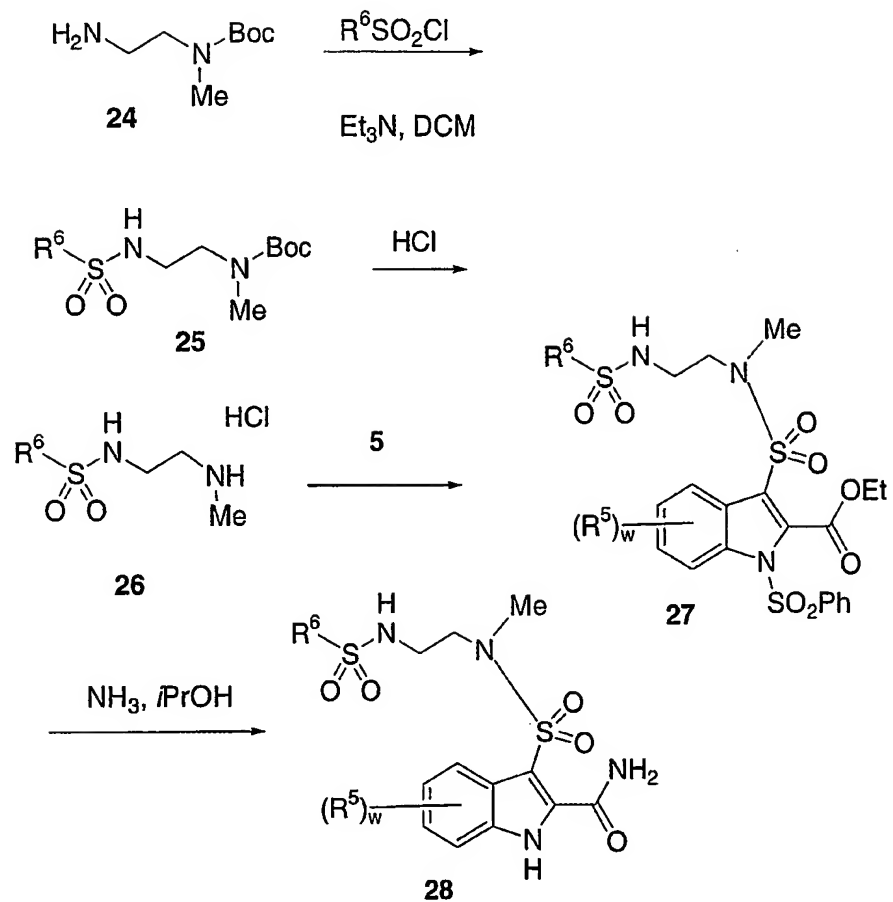
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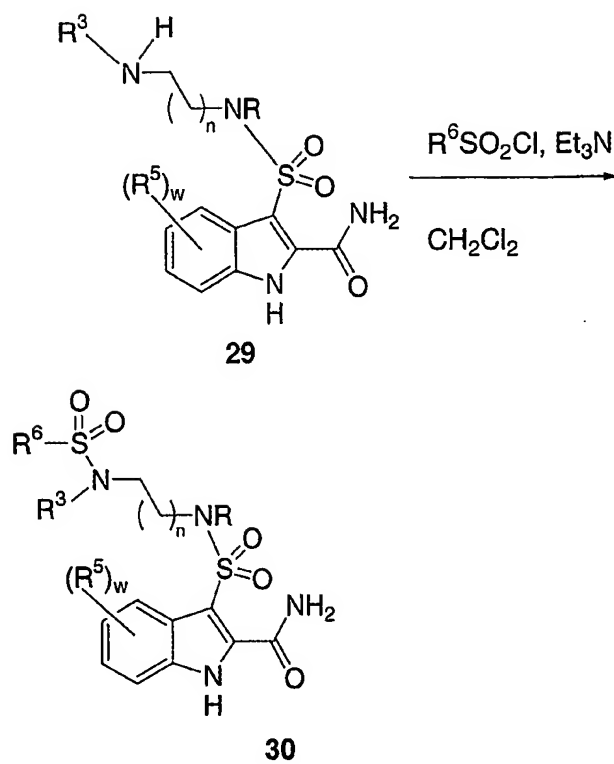


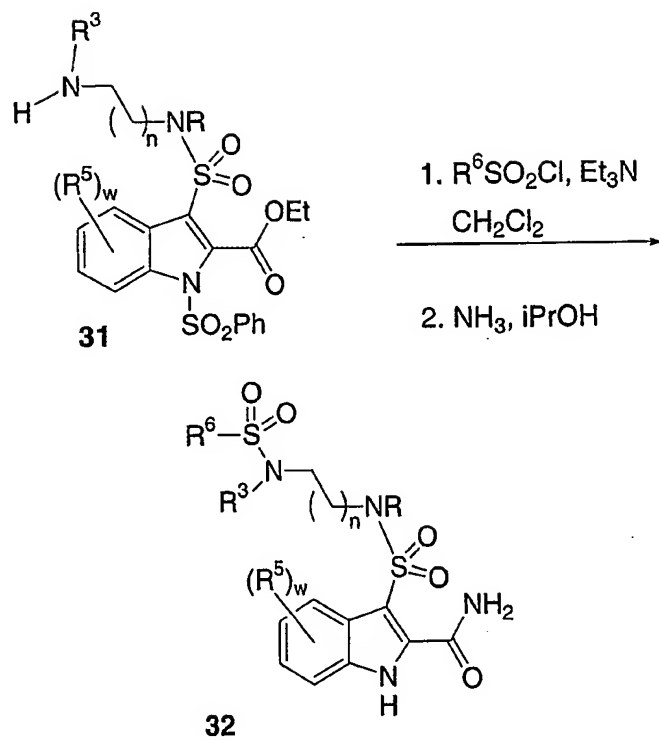
SCHEME 7

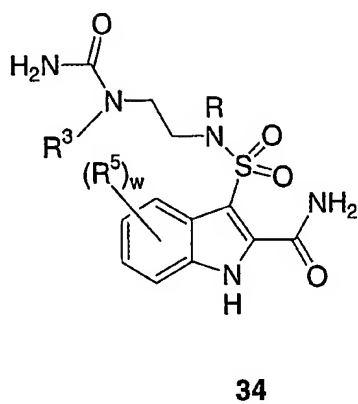
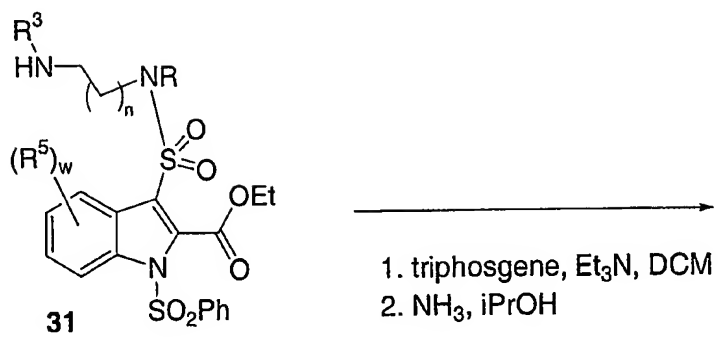


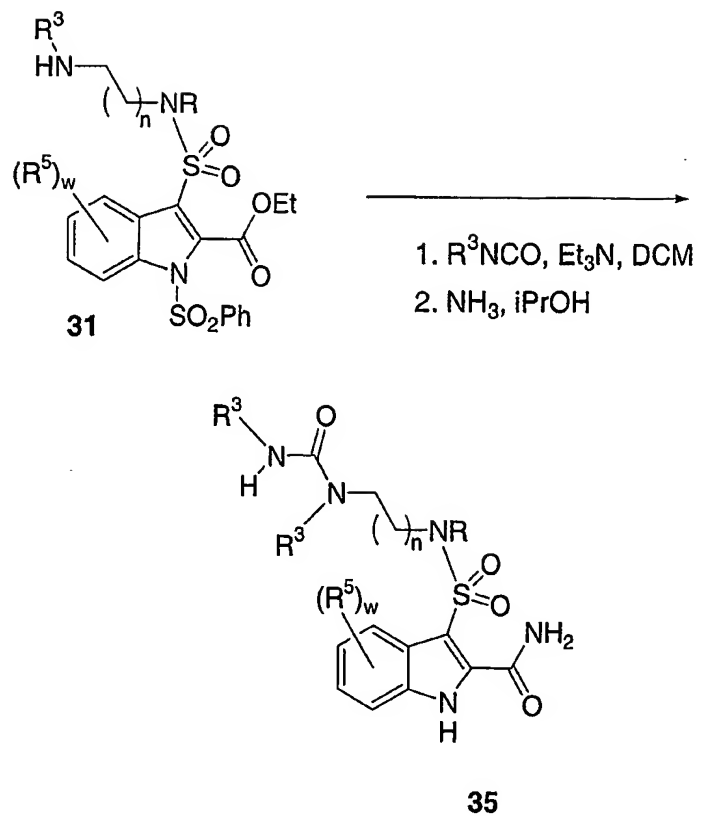
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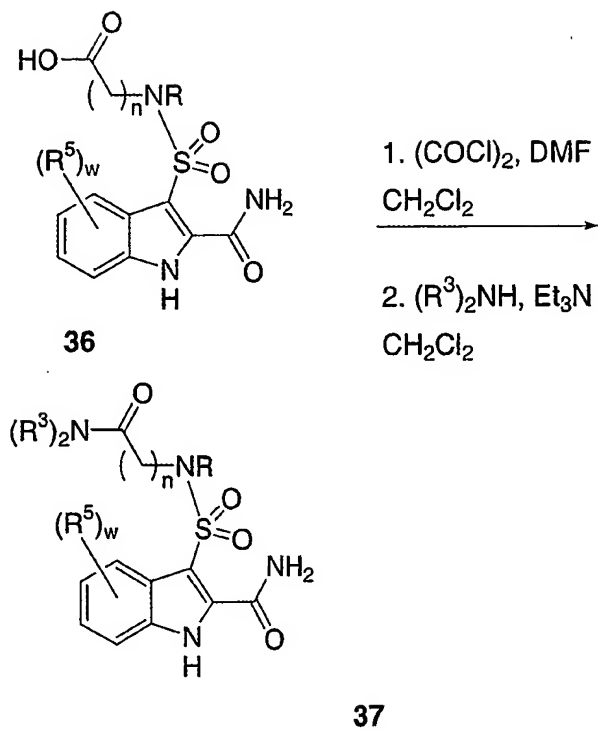


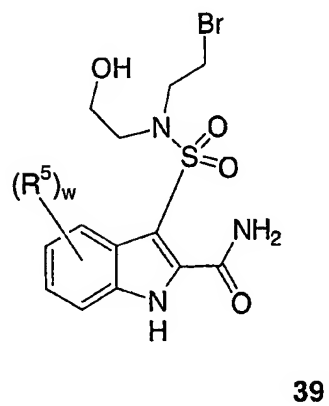
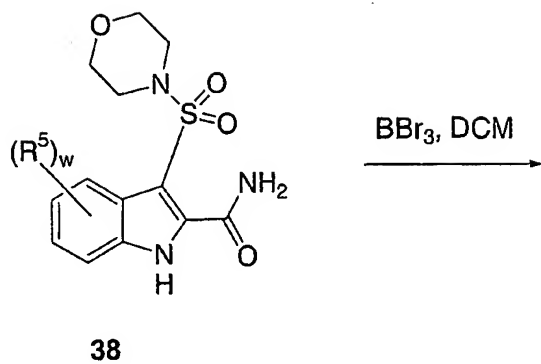
SCHEME 9

SCHEME 10

SCHEME 12

SCHEME 13

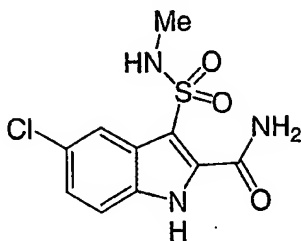
SCHEME 14

SCHEME 15

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limiting of the reasonable scope thereof.

EXAMPLE 1

10 5-Chloro-3-[(methylamino)sulfonyl]-1H-indole-2-carboxamideStep A: Ethyl 5-chloro-1-(phenylsulfonyl)-1H-indole-2-carboxylate

A 60% dispersion of NaH in mineral oil (1.07 g, 26.9 mmol) was washed with hexane, and the resulting powder was suspended in 40 mL of DMF. After cooling the stirred mixture to 0 °C, ethyl 5-chloro-1H-indole-2-carboxylate (5.00 g, 22.4 mmol) was added in portions. The solution was warmed to room temperature, during which gas was released. After 15 minutes, the mixture was cooled again to 0 °C, and benzenesulfonyl chloride was added dropwise (3.14 mL, 24.6 mmol). After warming to room temperature, the reaction was stirred for 1.5 hours, then poured into a mixture of EtOAc and saturated aqueous NaHCO₃ solution. The organic phase was washed with water and brine, dried with Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting solid was stirred in 50 mL of a 10% EtOAc/hexane solution for 30 minutes, then filtered to provide the titled product as a white powder. Proton NMR for the product was consistent with the titled compound.

ESI+ MS: 364.1 [M+H]⁺.

Step B: 5-Chloro-2-(ethoxycarbonyl)-1-(phenylsulfonyl)-1*H*-indole-3-sulfonic
acid

To a solution of ethyl 5-chloro-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (5.56 g, 15.3 mmol) in 50 mL of dichloromethane at 0 °C was added
5 acetic anhydride (7.23 mL, 76.6 mmol), followed by dropwise addition of concentrated sulfuric acid. The solution was warmed to room temperature, stirred for 3 hours, and partitioned between 0.5 L of EtOAc and 0.5 L of 3N HCl solution. The organic phase was washed with brine, dried with Na₂SO₄, filtered, and concentrated *in vacuo*. The product was reconcentrated from benzene *in vacuo* to give the titled
10 product as a yellow solid. Proton NMR for the product was consistent with the titled compound of the formula C₁₇H₁₄ClNO₇S₂•0.5 CH₃CO₂H. ESI+ MS: 444.0 [M+H]⁺, 466.0 [M+Na]⁺.

Step C: Ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-
15 carboxylate

To a solution of the 5-chloro-2-(ethoxycarbonyl)-1-(phenylsulfonyl)-1*H*-indole-3-sulfonic acid (9.52 g, 21.4 mmol) in 100 mL of dichloromethane at 0 °C was added oxalyl chloride (5.61 mL, 64.3 mmol). Dimethylformamide (0.2 mL) was added, and the reaction was allowed to warm to room temperature. After 24 hours,
20 another portion of oxalyl chloride (3.0 mL) was added, and the reaction was stirred for an additional 16 hours. The mixture was concentrated *in vacuo* to provide a yellow foam. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 426.2 [M-Cl]⁺.

Step D: Ethyl 5-chloro-3-[(methylamino)sulfonyl]-1-(phenylsulfonyl)-1*H*-
25 indole-2-carboxylate

To a solution of ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (101 mg, 0.219 mmol) in 2 mL of dichloromethane was added triethylamine (0.157 mL, 1.09 mmol), followed by
30 methylamine hydrochloride (44 mg, 0.66 mmol). After one hour, the mixture was partitioned between 100 mL of EtOAc and 100 mL of saturated aqueous NH₄Cl solution. The organic phase was washed with brine, dried with Na₂SO₄, filtered, and concentrated *in vacuo* to give the titled product. ESI+ MS: 457.0 [M+H]⁺.

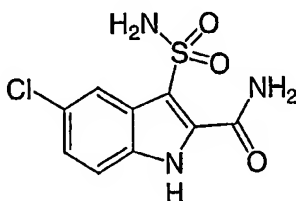
Step E: 5-Chloro-3-[(methylamino)sulfonyl]-1*H*-indole-2-carboxamide

A sealed tube was charged with ethyl 5-chloro-3-
[(methylamino)sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (ca. 0.22 mmol)
and 5 mL of isopropanol. The solution was cooled in an ice bath, and ammonia gas
was bubbled through the solution for 5 minutes. The tube was sealed, and heated at
100 °C for 3 days. The mixture was concentrated *in vacuo*, taken up in 0.5 mL of
80% DMF/water solution, filtered, and purified by preparative reverse phase HPLC to
afford the titled product. HRMS (ES) exact mass calculated for C₁₀H₁₁ClN₃O₃S
(M+H⁺): 288.0204. Found 288.0205.

10

EXAMPLE 2

3-(Aminosulfonyl)-5-chloro-1*H*-indole-2-carboxamide

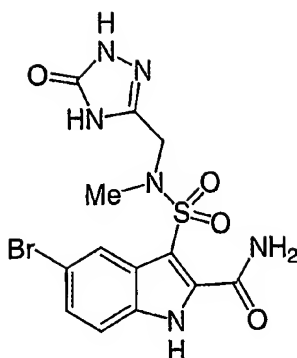


Following the procedure described in Step E of Example 1, replacing
ethyl 5-chloro-3-[(methylamino)sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate
with ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate
(from step C of Example 1), the title compound was obtained. HRMS (ES) exact
mass calculated for C₉H₁₂ClN₄O₃S (M+NH₄⁺): 291.0313. Found 291.0300.

20

EXAMPLE 3

5-Bromo-3-({methyl[(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]amino}sulfonyl)-1*H*-indole
carboxamide



Step A: Ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

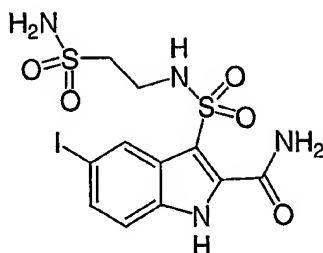
Following the procedures described in Steps A-C of Example 1, replacing ethyl 5-chloro-1*H*-indole-2-carboxylate with ethyl 5-bromo-1*H*-indole-2-carboxylate in Step A, the title compound was obtained. ESI+ MS: 505.0 [M+H]⁺.

Step B: 5-Bromo-3-({methyl[(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)methyl]amino}sulfonyl)-1*H*-indole-2-carboxamide

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with 5-[(methylamino)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one, (prepared using the method of T. Ladduwahetty et al., *J. Med. Chem* **1996**, 39, 2907-2914) the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₃H₁₄BrN₆O₄S (M+H⁺): 428.9975. Found 428.9974.

EXAMPLE 4

3-({[2-(Aminosulfonyl)ethyl]amino}sulfonyl)-5-iodo-1*H*-indole-2-carboxamide



Step A: Ethyl 3,5-diiodo-1H-indole-2-carboxylate

Ethyl indole-2-carboxylate (5.00 g, 26.4 mmol), iodine (6.71 g, 26.4 mmol), sodium periodate (2.82 g, 13.2 mmol) and concentrated sulfuric acid (2.94 mL, 52.8 mmol) were combined in 50 mL of absolute ethanol and heated to reflux for 1.5 hours. The vessel was cooled to ambient temperature and poured into a biphasic mixture of ethyl acetate (100 mL) and saturated aqueous sodium sulfite (100 mL) solution. The organic layer was removed and the aqueous layer was further extracted twice with ethyl acetate. The combined organic extracts were washed once with aqueous saturated NaCl, dried with Na₂SO₄, filtered and concentrated *in vacuo* to provide the title product. ESI+ MS: 441.8 [M+H]⁺.

Step B: Ethyl 5-iodo-1H-indole-2-carboxylate

Ethyl 3,5-diiodo-1H-indole-2-carboxylate (12.1 g, 26.4 mmol) was suspended in 250 mL of absolute ethanol, to which concentrated aqueous hydrogen chloride (22.0 mL, 264 mmol) was added. Zinc dust (17.3 g, 264 mmol) was added portionwise over 30 minutes. After stirring for 45 minutes, two additional portions of zinc were added slowly (5.2 and 4.4 g, 146 mmol). After stirring for 30 minutes, the mixture was poured into water and extracted four times with ethyl acetate. The combined organic extracts were washed once with aqueous saturated NaHCO₃ and once with aqueous saturated NaCl. The organic extract was dried with Na₂SO₄, filtered and concentrated *in vacuo*. The residue was crystallized three times from hexanes and ethyl acetate, providing the title compound. The mother liquor was columned by flash chromatography (0 to 8% ethyl acetate in hexanes) to provide an additional amount of the title compound. HRMS (ES) exact mass calculated for C₁₁H₁₀INO₂ (M+Na⁺): 377.9648. Found 377.9649.

Step C: Ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate

Following the procedures described in Steps A-C of Example 1, replacing ethyl 5-chloro-1*H*-indole-2-carboxylate with ethyl 5-iodo-1*H*-indole-2-carboxylate in Step A, the title compound was obtained. ESI+MS: 518.07 [M-Cl]⁺.

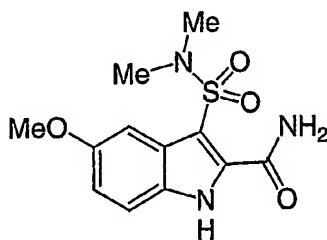
5 Step D: 5-Iodo-3-([2-(aminosulfonyl)ethyl]amino)sulfonyl)-1*H*-indole-2-carboxamide

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with 2-aminoethanesulfonamide hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+MS: 473.0 [M+H]⁺.

EXAMPLE 5

15

3-[(Dimethylamino)sulfonyl]-5-methoxy-1*H*-indole-2-carboxamide



Step A: Ethyl 3-(chlorosulfonyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

20 Following the procedures described in Steps A-C of Example 1, replacing ethyl 5-chloro-1*H*-indole-2-carboxylate with ethyl 5-methoxy-1*H*-indole-2-carboxylate in Step A, the title compound was obtained. ESI+ MS: 408.0 [M-Cl]⁺.

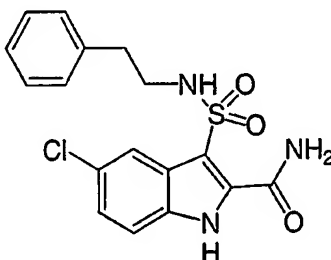
Step B: 3-[(Dimethylamino)sulfonyl]-5-methoxy-1*H*-indole-2-carboxamide

25 Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 3-(chlorosulfonyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with dimethylamine 2.0 M solution in

tetrahydrofuran, and omitting triethylamine from the reaction mixture, the title compound was obtained. ESI+ MS: 298.2 [M+H]⁺.

EXAMPLE 6

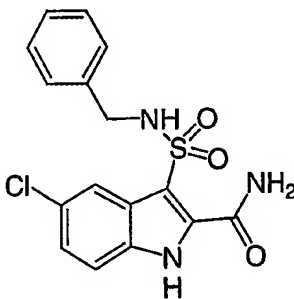
5

5-Chloro-3-[(2-phenethyl)amino]sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with phenethylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₇H₁₇ClN₃O₃S (M+H⁺): 378.0674. Found 378.0678.

EXAMPLE 7

15

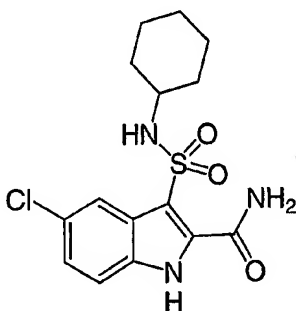
5-Chloro-3-[(benzylamino)sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with benzylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound.

HRMS (ES) exact mass calculated for $C_{16}H_{15}ClN_3O_3S$ ($M+H^+$): 363.0517. Found 363.0504.

EXAMPLE 8

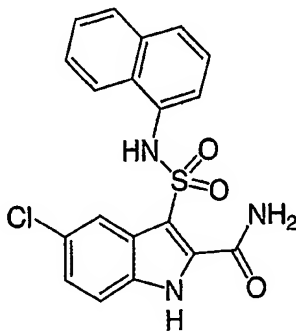
5

5-Chloro-3-[(cyclohexylamino)sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with cyclohexylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{15}H_{19}ClN_3O_3S$ ($M+H^+$): 356.0830. Found 356.0835.

15

EXAMPLE 9

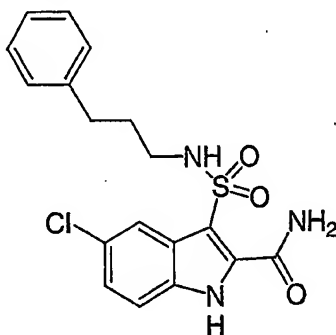
5-Chloro-3-[(1-naphthylamino)sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 1-naphthylamine, the title

compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{19}H_{15}ClN_3O_3S$ ($M+H^+$): 400.0517. Found 400.0523.

5

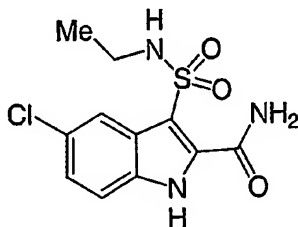
EXAMPLE 10

5-Chloro-3-([(3-phenylpropyl)amino]sulfonyl)-1H-indole-2-carboxamide

10 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 3-phenylpropylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{18}H_{19}ClN_3O_3S$ ($M+H^+$): 392.0830. Found 392.0837.

15

EXAMPLE 11

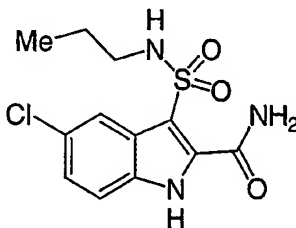
5-Chloro-3-[(ethylamino)sulfonyl]-1H-indole-2-carboxamide

20 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with ethylamine hydrochloride, the

title compound was obtained. HRMS (ES) exact mass calculated for $C_{11}H_{13}ClN_3O_3S$ ($M+H^+$): 302.0361. Found 302.0350.

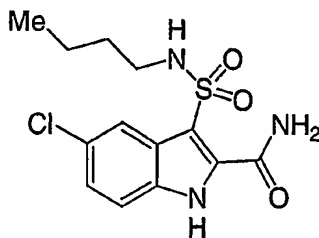
EXAMPLE 12

5

5-Chloro-3-[(propylamino)sulfonyl]-1H-indole-2-carboxamide

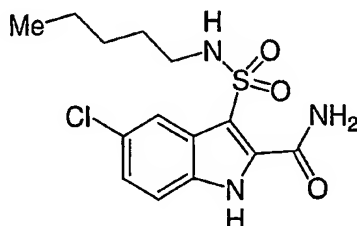
Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with propylamine, the title compound was obtained. HRMS (ES) exact mass calculated for $C_{12}H_{15}ClN_3O_3S$ ($M+H^+$): 316.0512. Found 316.0499.

EXAMPLE 13

15 5-Chloro-3-[(butylamino)sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with butylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{13}H_{17}ClN_3O_3S$ ($M+H^+$): 330.0674. Found 330.0670.

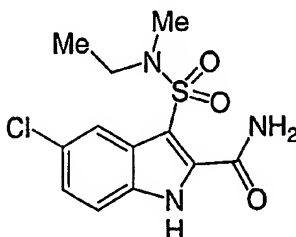
EXAMPLE 14

5-Chloro-3-[(pentylamino)sulfonyl]-1H-indole-2-carboxamide

5 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with pentylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{14}H_{19}ClN_3O_3S$ ($M+H^+$): 344.0830. Found 344.0825.

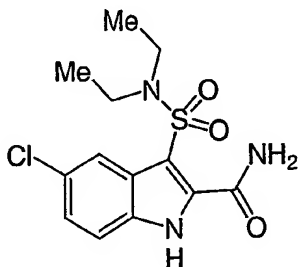
10

EXAMPLE 15

5-Chloro-3-[[ethyl(methyl)amino]sulfonyl]-1H-indole-2-carboxamide

15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with ethyl(methyl)amine, the title compound was obtained.
 H^1 -NMR (500 MHz, CD_3OD) δ 8.07 (d, $J = 2.0$ Hz, 1H), 7.53 (d, $J = 8.8$ Hz, 1H), 7.34 (dd, $J = 8.8, 2.2$ Hz, 1H), 3.13 (q, $J = 7.2$ Hz, 2H), 2.74 (s, 3H), 1.09 (t, $J = 7.1$
20 Hz, 3H) ppm. HRMS (ES) exact mass calculated for $C_{12}H_{15}ClN_3O_3S$ ($M+H^+$): 316.0517. Found 316.0518.

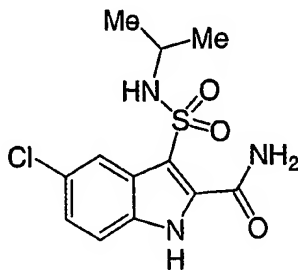
EXAMPLE 16

5-Chloro-3-[(diethylamino)sulfonyl]-1H-indole-2-carboxamide

5 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with diethylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{13}H_{17}ClN_3O_3S$ ($M+H^+$): 330.0674. Found 330.0672.

10

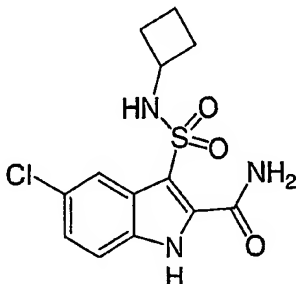
EXAMPLE 17

5-Chloro-3-[(*iso*-propylamino)sulfonyl]-1H-indole-2-carboxamide

15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with *iso*-propylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{12}H_{15}ClN_3O_3S$ ($M+H^+$): 316.05817. Found 316.0519.

20

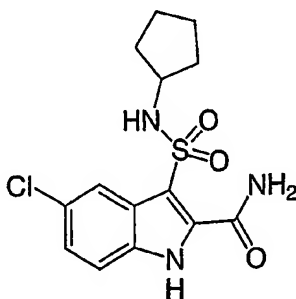
EXAMPLE 18

5-Chloro-3-[(cyclobutylamino)sulfonyl]-1H-indole-2-carboxamide

5 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with cyclobutylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{13}H_{15}ClN_3O_3S$ ($M+H^+$): 328.0517. Found 328.0516.

10

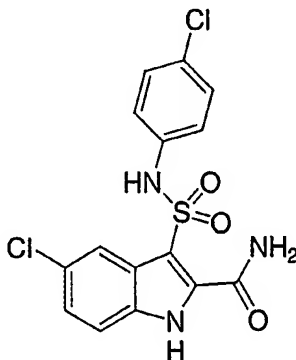
EXAMPLE 19

5-Chloro-3-[(cyclopentylamino)sulfonyl]-1H-indole-2-carboxamide

15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with cyclopentylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{14}H_{17}ClN_3O_3S$ ($M+H^+$): 342.0674. Found 342.0675.

20

EXAMPLE 20

5-Chloro-3-[[4-(4-chlorophenyl)amino]sulfonyl]-1H-indole-2-carboxamide

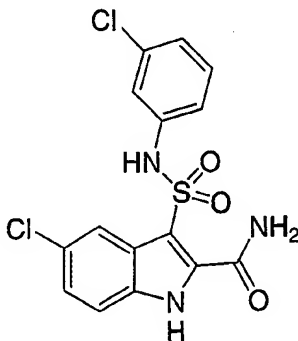
5 Step A: Ethyl 5-chloro-3-[[4-(4-chlorophenyl)amino]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

To a 0 °C solution of ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate (200 mg, 0.43 mmol) in 3 mL of dichloromethane was added triethylamine (0.120 mL, 0.86 mmol), followed by 4-chloroaniline (66 mg, 0.52 mmol). This was stirred for 15 minutes, warmed to room temperature and stirred overnight. The mixture was partitioned between of EtOAc and saturated aqueous NaHCO₃ solution, and the organic phase was concentrated *in vacuo*. The residue was taken up in a minimal amount of CH₂Cl₂, decanted from precipitate and concentrated *in vacuo*. This was taken up in EtOAc and washed with 15 1N HCl, saturated NaHCO₃ solution, and brine. The solution was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by preparative TLC gave the titled product. ESI+ MS: 553.0 [M+H]⁺.

20 Step B: 5-Chloro-3-[[4-(4-chlorophenyl)amino]sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Step E of Example 1, replacing ethyl 5-chloro-3-[(methylamino)sulfonyl]-1-(phenylsulfonyl)-1H-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated 25 for C₁₅H₁₂Cl₂N₃O₃S [M+H]⁺: 383.9971. Found 383.9961.

EXAMPLE 21

5-Chloro-3-[[(3-chlorophenyl)amino]sulfonyl]-1H-indole-2-carboxamide

- 5 Step A: Ethyl 5-chloro-3-[[(3-chlorophenyl)amino]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

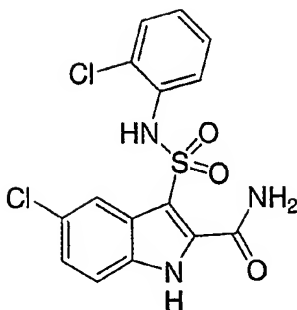
To a solution of ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate (100 mg, 0.22 mmol) in 2 mL of dichloromethane was added triethylamine (0.061 mL, 0.44 mmol), followed by 3-chloroaniline (0.025 mL, 0.24 mmol). This was stirred at room temperature overnight. The reaction was heated in a sealed tube to 65 °C for 5 hours and then 50°C overnight. This was poured into EtOAc and washed with 1N HCl, saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo*. ESI+ MS: 553.0 [M+H]⁺.

- 15 Step B: 5-Chloro-3-[[(3-chlorophenyl)amino]sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Step E of Example 1, replacing ethyl 5-chloro-3-[(methylamino)sulfonyl]-1-(phenylsulfonyl)-1H-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 384.1 [M+H]⁺.

EXAMPLE 22

5-Chloro-3-[[(2-chlorophenyl)amino]sulfonyl]-1H-indole-2-carboxamide



Step A: Ethyl 5-chloro-3-((2-chlorophenyl)amino)-1-(phenylsulfonyl)-1H-indole-2-carboxylate

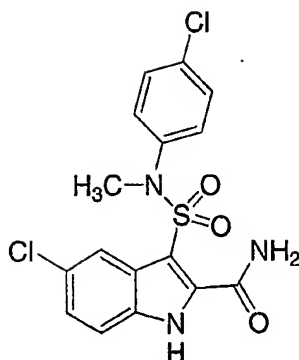
Following the procedure described in Example 21, Step A, replacing the 3-chloroaniline with 2-chloroaniline, the titled compound was obtained. ESI+ MS: 553.0 [M+H]⁺.

Step B: 5-Chloro-3-((3-chlorophenyl)amino)sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Step E of Example 1, replacing ethyl 5-chloro-3-((methylamino)sulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ¹H NMR (500 MHz, DMSO-*d*⁶) δ 7.98 (br s, 1H), 7.60 (br d, *J*=7.5 Hz, 1H), 7.38 (d, *J*=9.1 Hz, 1H), 7.28 (br d, *J*=8.8 Hz, 1H), 7.22 (br t, *J*=7.3 Hz, 1H), 7.16, (br d, *J*=8.1 Hz, 1H), 7.07 (br t, *J*=7.4 Hz, 1H) ppm. HRMS (ES) exact mass calculated for C₁₅H₁₂Cl₂N₃O₃S [M+H]⁺: 383.9971. Found 383.9962.

EXAMPLE 23

5-Chloro-3-((4-chlorophenyl)methylamino)sulfonyl]-1H-indole-2-carboxamide



Step A: Ethyl 5-chloro-3-([(4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

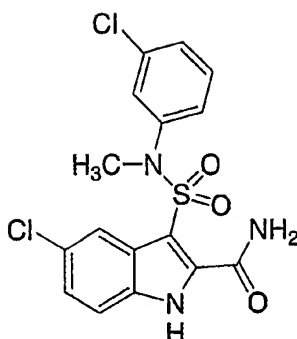
In 2 mL of dichloromethane, ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate (100 mg, 0.22 mmol), 4-chloro-N-methylaniline (0.029mL, 0.24 mmol) and triethylamine (0.061mL, 0.44 mmol) were combined in a sealed tube and heated to 65 °C for 4 hours and stirred at room temperature overnight. The reaction was poured into EtOAc and washed with 1N HCl, saturated NaHCO₃ solution and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo* to give the titled product. ESI+ MS: 567.0 [M+H]⁺.

Step B: 5-Chloro-3-([(3-chlorophenyl)amino]sulfonyl)-1H-indole-2-carboxamide

Following the procedure described in Step E of Example 1, replacing ethyl 5-chloro-3-[(methylamino)sulfonyl]-1-(phenylsulfonyl)-1H-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 398.0 [M+H]⁺.

EXAMPLE 24

5-Chloro-3-([(3-chlorophenyl)methylamino]sulfonyl)-1H-indole-2-carboxamide



Step A: Ethyl 5-chloro-3-([(3-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

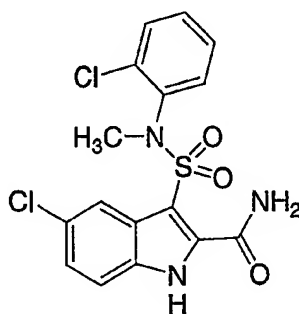
Following the procedure described in Step A of Example 23, replacing 4-chloro-N-methylaniline with 3-chloro-N-methylaniline, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 567 [M+H]⁺.

Step B: 5-Chloro-3-([(3-chlorophenyl)amino]sulfonyl)-1H-indole-2-carboxamide

Following the procedure described in Step B of Example 23, replacing ethyl 5-chloro-3-([(4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1H-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 398.0 [M+H]⁺.

EXAMPLE 25

5-Chloro-3-([(2-chlorophenyl)methylamino]sulfonyl)-1H-indole-2-carboxamide



Step A: Ethyl 5-chloro-3-([(2-chlorophenyl)methylamino]-1-(phenylsulfonyl)-
1*H*-indole-2-carboxylate

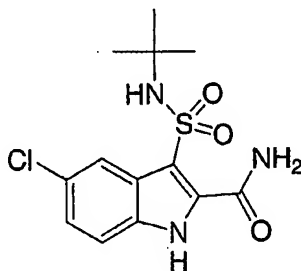
Following the procedure described in Step A of Example 23, replacing 4-chloro-*N*-methylaniline with 2-chloro-*N*-methylaniline, the titled compound was obtained. Proton NMR for the product was consistant with the titled compound.
ESI+ MS: 567 [M+H]⁺.

Step B: 5-Chloro-3-([(3-chlorophenyl)amino]sulfonyl)-1*H*-indole-2-carboxamide

Following the procedure described in Step B of Example 23, replacing ethyl 5-chloro-3-([(4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistant with the titled compound. ESI+ MS: 398.0 [M+H]⁺.

EXAMPLE 26

5-Chloro-3-[(*tert*-butylamino)sulfonyl]-1*H*-indole-2-carboxamide



Step A: Ethyl 5-chloro-3-[(*tert*-butylamino)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

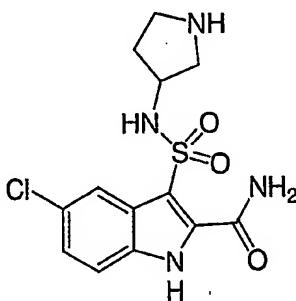
To a solution of the product from example 1, Step C (100mg, 0.22 mmols) in 2 mL of CH₂Cl₂, *tert*-butylamine (0.025mL, 0.24 mmol) and triethylamine (0.061 mL, 0.44 mmol) were added. The reaction was stirred overnight at room temperature, then poured into EtOAc, washed with 1N HCl, saturated NaHCO₃ solution and brine. Dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 499 [M+H]⁺.

Step B: 5-Chloro-3-[(*tert*-butylamino)sulfonyl]-1*H*-indole-2-carboxamide

- Following the procedure described in Step B of Example 23, replacing ethyl 5-chloro-3-[[4-(4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 352.0 [M+Na]⁺.

EXAMPLE 27

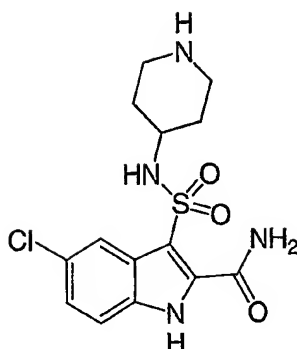
10 (±)-5-Chloro-3-[(pyrrolidin-3-ylamino)sulfonyl]-1*H*-indole-2-carboxamide



- Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with (±)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₃H₁₆ClN₄O₃S (M+H⁺): 343.0626. Found 343.0622.

EXAMPLE 28

20 5-Chloro-3-[(piperidin-4-ylamino)sulfonyl]-1*H*-indole-2-carboxamide

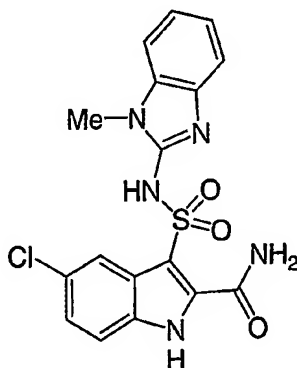


Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with *tert*-butyl 4-aminopiperidine-1-carboxylate, the title compound was obtained. Proton NMR for the product was
 5 consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{14}H_{18}ClN_4O_3S$ ($M+H^+$): 357.0783. Found 357.0780.

10

EXAMPLE 29

5-Chloro-3-{[(1-methyl-1*H*-benzimidazol-2-yl)amino]sulfonyl}-1*H*-indole-2-
carboxamide



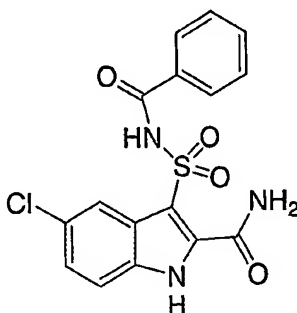
15

Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 1-methyl-1*H*-benzimidazol-2-amine, the title compound was obtained. Proton NMR for the product was consistent

with the titled compound. HRMS (ES) exact mass calculated for $C_{17}H_{16}ClN_5O_3S$ ($M+H^+$): 404.0579. Found 404.0577.

EXAMPLE 30

5

5-Chloro-3-[(benzamideamino)sulfonyl]-1H-indole-2-carboxamide

Step A: Ethyl 5-chloro-3-(aminosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate

10 Through a 0 °C solution of the product from Example 1, Step C (96 mg, 0.21 mmols) in 5 mL of CH_2Cl_2 , ammonia gas was bubbled for 3 minutes. The reaction was sealed, stirred for 30 minutes, warmed to room temperature and stirred 20 minutes more. This was poured into EtOAc and washed with water and brine. The solution was dried over Na_2SO_4 and concentrated *in vacuo* to give the titled
15 compound. ESI+ MS: 443 [$M+H$]⁺.

Step B: Ethyl 5-chloro-3-[(benzamideamino)sulfonyl]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

20 In 3 mL of CH_2Cl_2 , the product from Step A above (77 mg, 0.17 mmol) was combined with benzoic acid (21 mg, 0.17 mmol), EDC (33 mg, 0.17 mmol) and dimethylaminopyridine (21 mg, 0.17 mmol) and stirred overnight at room temperature. The reaction was diluted with EtOAc, washed with 1N HCl, saturated $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and concentrated *in vacuo* to give the titled compound. ESI+ MS: 547.0 [$M+H$]⁺.

25

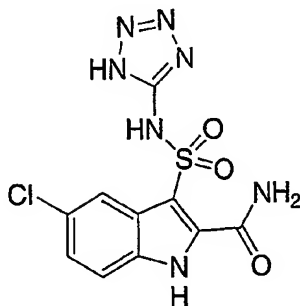
Step C: 5-Chloro-3-[(benzamideamino)sulfonyl]-1H-indole-2-carboxamide

Following the procedure described in Step B of Example 23, replacing ethyl 5-chloro-3-[[4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with the product from Step B, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 378.0

5 [M+H]⁺.

EXAMPLE 31

5-Chloro-3-[(5-aminotetrazole)sulfonyl]-1*H*-indole-2-carboxamide



10

Step A: Ethyl 5-chloro-3-[(5-aminotetrazole)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

To a solution of the product from example 1, Step C (100 mg, 0.22 mmol) in 3 mL of CH₂Cl₂, 5-aminotetrazole (21 mg, 0.24 mmol) and triethylamine (0.046 mL, 0.33 mmol) were added. The reaction was stirred at room temperature for 2 hours, 7mg more aminotetrazole and 20μL triethylamine were added, and the reaction was allowed to stir overnight. The mixture was poured into EtOAc, washed with 1 N HCl, saturated NaHCO₃ solution and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 511 [M+H]⁺.

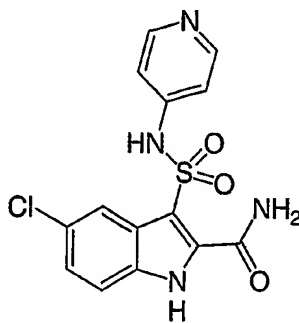
20

Step B: 5-Chloro-3-[(5-aminotetrazole)sulfonyl]-1*H*-indole-2-carboxamide

Following the procedure described in Step B of Example 23, replacing ethyl 5-chloro-3-[[4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 342 [M+H]⁺.

25

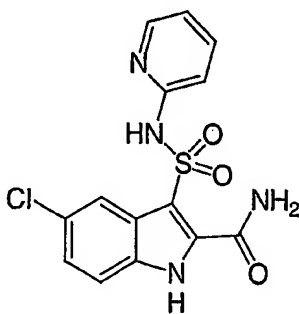
EXAMPLE 32

5-Chloro-3-[(pyridin-4-ylamino)sulfonyl]-1H-indole-2-carboxamide

5 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 4-aminopyridine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{14}H_{12}ClN_4O_3S$ ($M+H^+$): 351.0313. Found 351.0315.

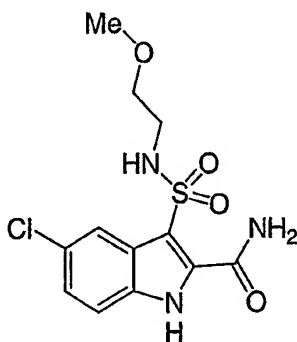
10

EXAMPLE 33

5-Chloro-3-[(pyridin-2-ylamino)sulfonyl]-1H-indole-2-carboxamide

15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 2-aminopyridine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 351.1 [$M+H$] $^+$.

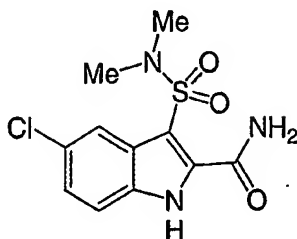
EXAMPLE 34

5-Chloro-3-[(2-methoxyethyl)amino]sulfonyl]-1H-indole-2-carboxamide

5 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 2-(methoxy)ethylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{12}H_{15}ClN_3O_4S$ ($M+H^+$): 332.0466. Found 332.0458.

10

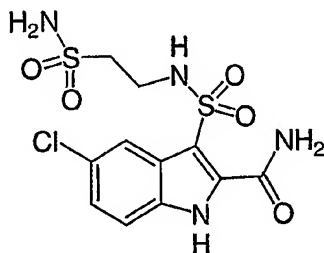
EXAMPLE 35

5-Chloro-3-[(dimethylamino)sulfonyl]-1H-indole-2-carboxamide

15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with dimethylamine hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{11}H_{13}ClN_3O_3S$ ($M+H^+$): 302.0361. Found 302.0335.

20

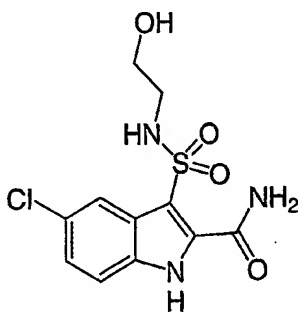
EXAMPLE 36

3-([2-(Aminosulfonyl)ethyl]amino)sulfonyl]-5-chloro-1H-indole-2-carboxamide

5 Following the procedures described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 2-aminoethanesulfonamide hydrochloride, the title compound was obtained. HRMS (ES) exact mass calculated for $C_{11}H_{14}ClN_4O_5S_2$ ($M+H^+$): 381.0089. Found 381.0116.

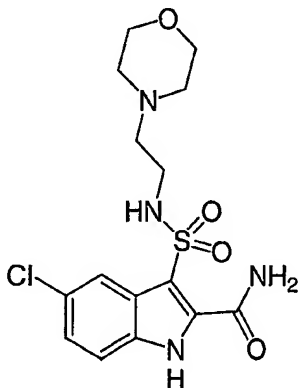
10

EXAMPLE 37

5-Chloro-3-([(2-hydroxyethyl)amino]sulfonyl)-1H-indole-2-carboxamide

15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 2-hydroxyethylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{11}H_{13}ClN_3O_4S$ ($M+H^+$): 318.0310. Found 318.0320.

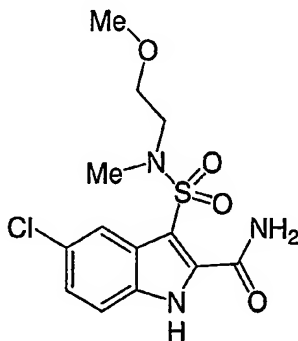
EXAMPLE 38

5-Chloro-3-([(2-morpholin-4-ylethyl)amino]sulfonyl)-1H-indole-2-carboxamide

5 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with 2-morpholin-4-ylethylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 387.1 [M+H]⁺.

10

EXAMPLE 39

5-Chloro-3-([(2-methoxyethyl)(methyl)amino]sulfonyl)-1H-indole-2-carboxamide

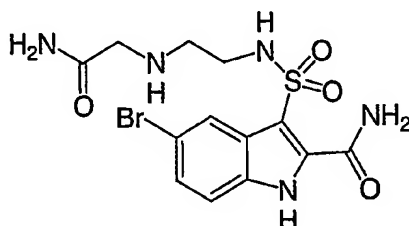
15 Following the procedure described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with *N*-(2-methoxyethyl)-*N*-methylamine, the title compound was obtained. Proton NMR for the product was

consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{13}H_{16}ClN_3O_4SNa$ ($M+Na^+$): 368.0442. Found 368.0440.

EXAMPLE 40

5

5-Bromo-3-[[[2-(2-acetamide)amino]ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide



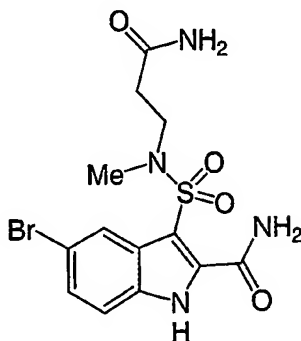
Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with methyl *N*-(2-aminoethyl)glycinate dihydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{13}H_{17}BrN_5O_4S$ ($M+H^+$): 418.0179. Found 418.0182.

15

EXAMPLE 41

N-{[2-(Aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl}-*N*-methyl-β-alaninamide

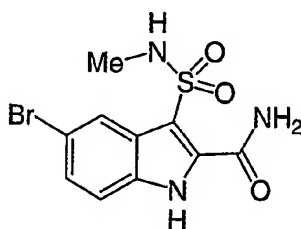
20



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with methyl *N*-methyl- β -alaninate hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 403.2 [M+H]⁺.

EXAMPLE 42

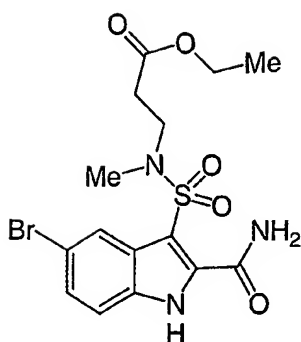
10 5-Bromo-3-[(methylamino)sulfonyl]-1*H*-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with methyl *N*-methyl- β -alaninate hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 332.2 [M+H]⁺.

EXAMPLE 43

20 Ethyl *N*-{[2-(aminocarbonyl)-5-bromo-1*H*-indol-3-yl]sulfonyl} *N*-methyl- β -alaninate

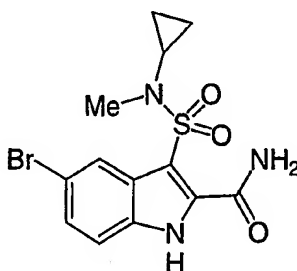


Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with methyl *N*-methyl-β-alaninate hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 432.2 [M+H]⁺.

EXAMPLE 44

10

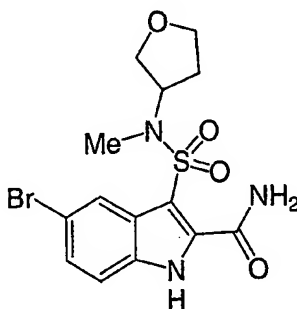
5-Bromo-3-[[cyclopropyl(methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with *N*-cyclopropyl-*N*-methylamine oxylate, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 372.2 [M+H]⁺.

EXAMPLE 45

(±)-5-Bromo-3-([methyl(tetrahydrofuran-3-yl)amino]sulfonyl)-1*H*-indole-2-carboxamide



5

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with (±)-*N*-methyl-*N*-tetrahydrofuran-3-ylamine, the title compound was obtained.

10

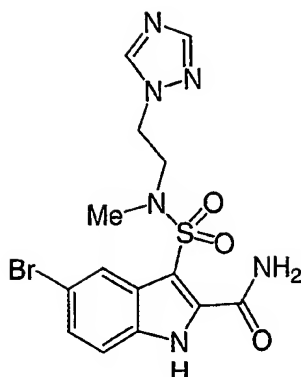
¹H NMR (500 MHz, DMSO-*d*⁶) δ 12.91 (br s, 1H), 8.29 (br s, 1H), 8.19 (br s, 1H), 8.04 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.47 (dd, *J* = 8.8, 1.7 Hz, 1H), 4.65 (m, 1H), 3.75 (m, 1H), 3.50 – 3.35 (m, 3H), 2.66 (s, 3H), 1.86 – 1.79 (m, 1H), 1.55 – 1.48 (m, 1H) ppm. ESI+ MS: 402.2 [M+H]⁺.

15

EXAMPLE 46

5-Bromo-3-([methyl[2-(1*H*-1,2,4-triazol-1-yl)ethyl]amino]sulfonyl)-1*H*-indole-2-carboxamide

20

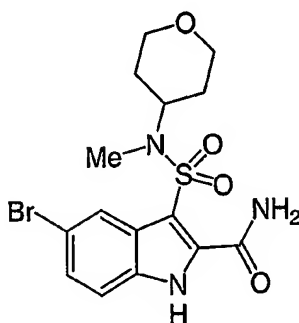


Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with *N*-methyl-*N*-[2-(1*H*-1,2,4-triazol-1-yl)ethyl]amine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 427.2 [M+H]⁺.

EXAMPLE 47

10

5-Bromo-3-{{methyl(tetrahydro-2*H*-pyran-4-yl)amino}sulfonyl}-1*H*-indole-2-carboxamide



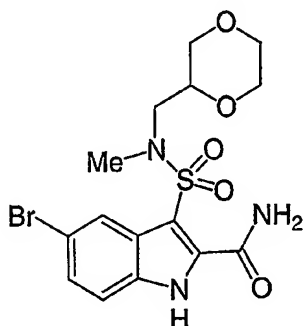
Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with *N*-methyl-*N*-(tetrahydro-2*H*-pyran-

4-yl)amine hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 416.2 [M+H]⁺.

EXAMPLE 48

5

(±)-5-Bromo-3-([(1,4-dioxan-2-ylmethyl)(methyl)amino]sulfonyl)-1*H*-indole-2-carboxamide

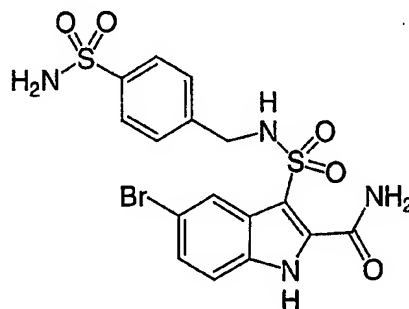


Following the procedures described in Steps D and E of Example 1,
 10 replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with (±)-*N*-methyl-*N*-(1,4-dioxan-2-ylmethyl)amine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 432.2 [M+H]⁺.

15

EXAMPLE 49

3-([(4-(Aminosulfonyl)benzyl)amino]sulfonyl)-5-bromo-1*H*-indole-2-carboxamide

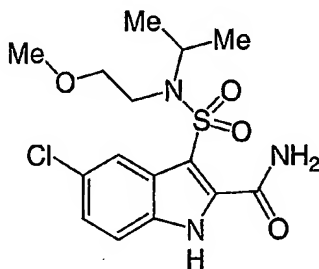


20

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with 4-(aminomethyl)benzenesulfonamide hydrochloride, the title compound was obtained. HRMS (ES) exact mass calculated for $C_{16}H_{16}BrN_4O_5S_2$ ($M+H^+$): 486.9740. Found 486.9749.

EXAMPLE 50

10 5-Chloro-3-{{*iso*-propyl(2-methoxyethyl)amino}sulfonyl}-1*H*-indole-2-carboxamide

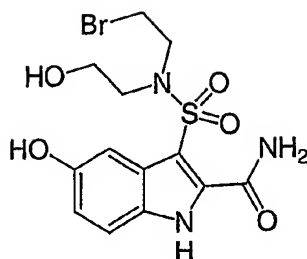


Following the procedures described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with *N*-(*iso*-propyl)-*N*-(2-methoxyethyl)amine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{15}H_{21}ClN_3O_4SNa$ ($M+Na^+$): 396.0755. Found 396.0755.

20

EXAMPLE 51

3-{{(2-Bromoethyl)(2-hydroxyethyl)amino}sulfonyl}-5-hydroxy-1*H*-indole-2-carboxamide



Step A: 5-Methoxy-3-(morpholin-4-ylsulfonyl)-1H-indole-2-carboxamide

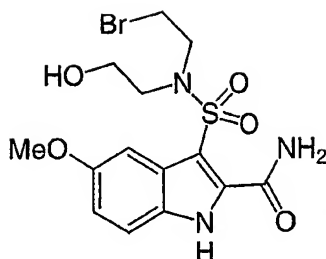
Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate with ethyl 3-(chlorosulfonyl)-5-methoxy-1-(phenylsulfonyl)-1H-indole-2-carboxylate, and methylamine hydrochloride and triethylamine with morpholine, the title compound was obtained. HRMS (ES) exact mass calculated for $C_{14}H_{18}N_3O_5S$ ($M+H^+$): 340.0962. Found 340.0960.

Step B: 3-([(2-Bromoethyl)(2-hydroxyethyl)amino]sulfonyl)-5-hydroxy-1H-indole-2-carboxamide

To a suspension of 5-methoxy-3-(morpholin-4-ylsulfonyl)-1H-indole-2-carboxamide (416 mg, 1.23 mmol) in 15 mL of dichloromethane at -78°C was added boron tribromide solution (1 M in dichloromethane, 6.13 mmol). After 10 minutes the mixture was allowed to warm to room temperature, and stir for an additional 60 hours. The reaction was poured into a mixture of EtOAc and saturated aqueous NaHCO_3 solution. The organic phase was washed with water and brine, dried with Na_2SO_4 , filtered, and concentrated *in vacuo*. Purification by flash chromatography through silica gel (3-10% MeOH/dichloromethane) provide the titled product, along with 5-hydroxy-3-(morpholin-4-ylsulfonyl)-1H-indole-2-carboxamide. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{13}H_{17}BrN_3O_5S$ ($M+H^+$): 406.0067. Found 406.0081.

EXAMPLE 52

3-([(2-Bromoethyl)(2-hydroxyethyl)amino]sulfonyl)-5-methoxy-1H-indole-2-carboxamide

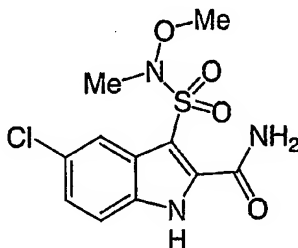


To a solution of 3-[[2-bromoethyl(2-hydroxyethyl)amino]sulfonyl]-5-hydroxy-1*H*-indole-2-carboxamide, described in Step B of Example 51, in 2:1 dichloromethane/MeOH was added excess trimethylsilyldiazomethane (solution in
 5 hexane). After stirring at room temperature for 16 hours, the mixture was concentrated in vacuo. Purification by preparative reversed phase HPLC afforded the titled product. HRMS (ES) exact mass calculated for C₁₄H₁₈BrN₃O₅S (M+H⁺): 420.0224. Found 420.0221.

10

EXAMPLE 53

5-Chloro-3-[[methoxy(methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide

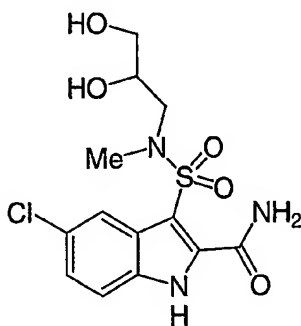


15

Following the procedures described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with *N*-methoxy-*N*-methylamine hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 318.1 [M+H]⁺.

EXAMPLE 54

(±)-5-Chloro-3-[[(2,3-dihydroxypropyl)(methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide



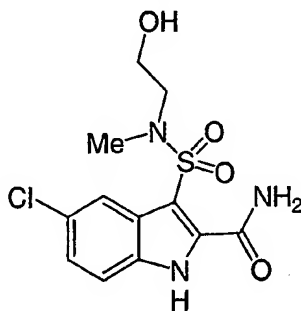
5

Following the procedures described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride and triethylamine with (±)-3-(methylamino)propane-1,2-diol, the title compound was obtained. HRMS (ES) exact mass calculated for C₁₃H₁₇ClN₃O₅S (M+H⁺): 362.0572. Found 362.0587.

10

EXAMPLE 55

5-Chloro-3-[[(2-hydroxyethyl)(methyl)amino]sulfonyl]-1*H*-indole-2-carboxamide

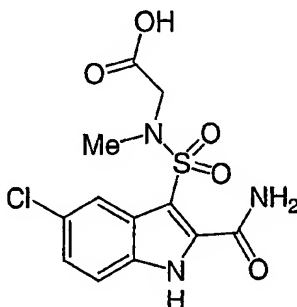


15

Following the procedures described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with *N*-(2-hydroxyethyl)-*N*-methylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 332.1 [M+H]⁺.

EXAMPLE 56

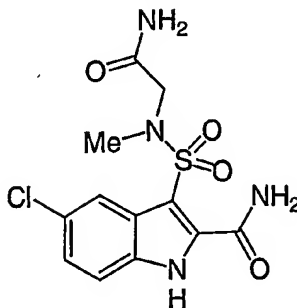
N-{[2-(Aminocarbonyl)-5-chloro-1*H*-indol-3-yl]sulfonyl}-*N*-methylglycine



- 5 The procedures described in Steps D and E of Example 1 were followed, replacing in Step D methylamine hydrochloride with sarcosine-*tert*-butyl ester hydrochloride. The product of Step E was purified by preparative reversed phase HPLC, then treated with 50% TFA/dichloromethane for 16 hours to give the titled compound. HRMS (ES) exact mass calculated for C₁₂H₁₃ClN₃O₅S (M+H⁺):
- 10 346.0259. Found 346.0259.

EXAMPLE 57

N-{[2-(Aminocarbonyl)-5-chloro-1*H*-indol-3-yl]sulfonyl}-*N*-methylglycinamide



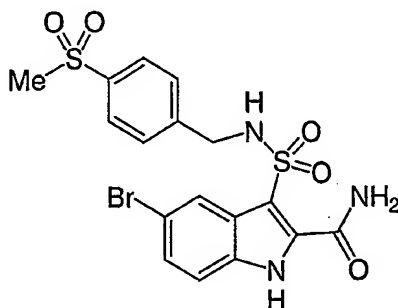
15

To a suspension of *N*-{[2-(Aminocarbonyl)-5-chloro-1*H*-indol-3-yl]sulfonyl}-*N*-methylglycine from Example 56 (10 mg, 0.029 mmol) in 1 mL of dichloromethane at room temperature was added oxalyl chloride (0.3 mL), followed by DMF (*ca.* 0.020 mL). After 20 minutes, the homogeneous mixture was

concentrated in vacuo to give a yellow solid. This was taken up in 1 mL of acetone, and a solution of 10% NH₄OH/acetone (2 mL) was added, whereupon a white precipitate formed. After two minutes, the solvent was decanted off, and the resulting solid was maintained *in vacuo* until dry. Purification by preparative reversed phase
 5 HPLC provided the titled compound as a white solid. ESI+ MS: 345.2 [M+H]⁺.

EXAMPLE 58

5-Bromo-3-({[4-(methylsulfonyl)benzyl]amino}sulfonyl)-1H-indole-2-carboxamide

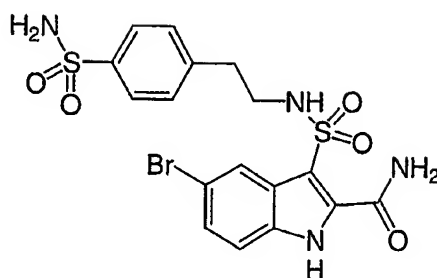


10

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate, and methylamine hydrochloride with 4-(methylsulfonyl)benzylamine
 15 hydrochloride, the title compound was obtained. HRMS (ES) exact mass calculated for C₁₇H₁₇BrN₃O₅S₂ (M+H⁺): 485.9788. Found 485.9784.

EXAMPLE 59

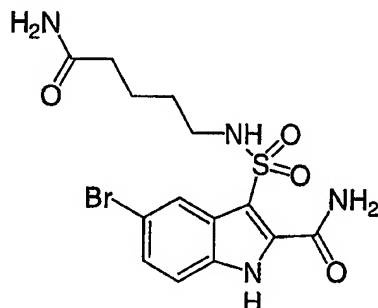
20 3-[(2-[4-(Aminosulfonyl)phenyl]ethyl)amino]sulfonyl]-5-bromo-1H-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with 4-(aminosulfonyl)benzene-sulfonamide hydrochloride, the title compound was obtained. HRMS (ES) exact mass calculated for $C_{17}H_{18}BrN_4O_5S_2$ ($M+H^+$): 500.9897. Found 500.9927.

EXAMPLE 60

3-[[[(5-Amino-5-oxopentyl)amino]sulfonyl]-5-bromo-1*H*-indole-2-carboxamide



Step A: Ethyl-5-bromo-3-[[[(5-*tert*-butoxy-5-oxopentyl)amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 3-(chlorosulfonyl)-5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with *tert*-butyl 5-aminopentanoate oxalic acid salt, the title compound was obtained after flash chromatography through silica gel (100% dichloromethane). ESI+ MS: 587 [$M-CH_2=CMe_2$] $^+$.

Step B: 5-Bromo-3-[[[(5-*tert*-butoxy-5-oxopentyl)amino]sulfonyl]-1*H*-indole-2-carboxylic acid

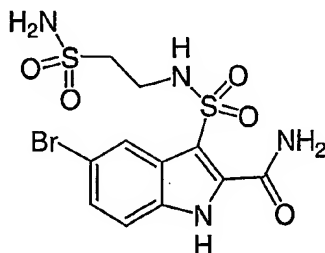
To a solution of ethyl-5-bromo-3-[[[(5-*tert*-butoxy-5-oxopentyl)amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (63 mg, 0.98 mmol) in 2 mL of 3:1 THF/water was added NaOH (2 pellets). After stirring at room temperature for 6 hours, another portion of NaOH was added. After 16 hours, the reaction was partitioned between 3N HCl and dichloromethane. The aqueous phase was extracted three times with dichloromethane, and the combined organic phases were dried (Na₂SO₄), filtered, and concentrated in vacuo to give the titled product as a white foam. ESI+ MS: 419 [M-CH₂=CMe₂]⁺.

Step C: 3-[[[(5-Amino-5-oxopentyl)amino]sulfonyl]-5-bromo-1*H*-indole-2-carboxamide

To a solution 5-bromo-3-[[[(5-*tert*-butoxy-5-oxopentyl)amino]sulfonyl]-1*H*-indole-2-carboxylic acid (47 mg, 0.098 mmol) in 3 mL of dichloromethane at room temperature was added trifluoroacetic acid (2 mL). After stirring for one hour at room temperature, the mixture was concentrated *in vacuo*. The resulting product was taken up in 3 mL of dichloromethane, and oxalyl chloride (0.2 mL) was added, followed by DMF (*ca.* 0.020 mL). After 10 minutes, the mixture was concentrated *in vacuo*. This was taken up in 3 mL of acetone, and a solution of 10% NH₄OH/acetone (5 mL) was added, whereupon a white precipitate formed. After two minutes, the reaction was concentrated *in vacuo*. Purification by preparative reversed phase HPLC provided the titled compound as a white powder. HRMS (ES) exact mass calculated for C₁₄H₁₈BrN₄O₄S (M+H⁺): 417.0227. Found 417.0233.

25

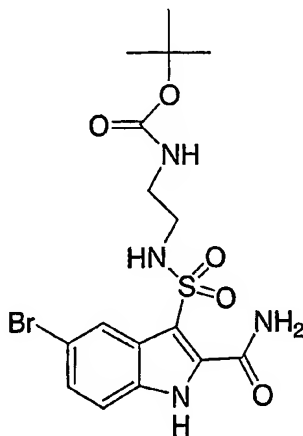
EXAMPLE 61

3-([2-(Aminosulfonyl)ethyl]amino)sulfonyl)-5-bromo-1H-indole-2-carboxamide

5 Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate, and methylamine hydrochloride with 2-aminoethanesulfonamide hydrochloride, the title compound was obtained as a white solid. HRMS (ES) exact
10 mass calculated for $C_{11}H_{13}BrN_4O_5S_2Na$ ($M+Na^+$): 446.9403. Found 446.9404.

EXAMPLE 62

15 *tert*-Butyl 2-([2-(aminocarbonyl)-5-bromo-1H-indol-3-yl]sulfonyl)amino)-ethylcarbamate



Step A: Ethyl 5-bromo-3-([2-([*tert*-butoxycarbonyl]amino)ethyl]amino)-sulfonyl]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

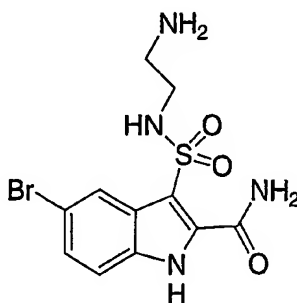
To a solution of the product from Example 3, Step A (400 mg, 0.789 mmols) in 5 mL of CH₂Cl₂, Boc-ethylenediamine (0.137 mL, 0.868 mmol) and triethylamine (0.22 mL, 1.6 mmol) were added. The reaction stirred at room temperature for 2 days, then poured into EtOAc, washed with saturated NaHCO₃ solution and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo*. Purification by flash chromatography using EtOAc:hexane (1:3) gave the titled compound. ESI+ MS: 530 [MH-Boc]⁺.

Step B: tert-Butyl 2-([2-(aminocarbonyl)-5-bromo-1H-indol-3-yl]sulfonyl)amino) ethylcarbamate

Following the procedure described in Step B of Example 23, replacing ethyl 5-chloro-3-([4-chlorophenyl)methylamino]-1-(phenylsulfonyl)-1H-indole-2-carboxylate with the product from Step A, the titled compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 361 [MH-Boc]⁺.

EXAMPLE 63

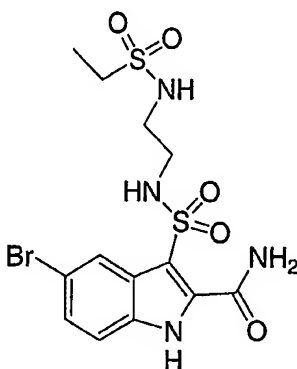
3-([2-(2-Aminoethyl)amino]sulfonyl)-5-bromo-1H-indole-2-carboxamide



Through a solution of the product from Example 62, Step B (113 mg, 0.245 mmols) in 20 mL of EtOAc at 0 °C was bubbled HCl gas for 3 minutes. The reaction was sealed, and stirring continued for 45 minutes. The solvent was removed *in vacuo* to give the titled compound. ESI+ MS: 361 [M+H]⁺.

EXAMPLE 64

5-Bromo-3-[[{(ethylsulfonylamino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide



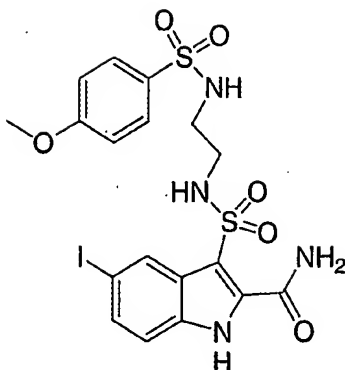
5

A solution of the product from Example 63 (15 mg, 0.038 mmol), triethylamine (0.017 mL, 0.11 mmol) and ethanesulfonyl chloride (0.004 mL, 0.04 mmols) were combined in a sealed tube and heated to 65 °C overnight. The solvent was removed under a stream of N₂ and replaced with DMF. After adding an additional 3 equivalents of ethanesulfonyl chloride and triethylamine, the reaction was heated to 65 °C for 8 hours and stirred at room temperature for 60 hours. The mixture was diluted with EtOAc and washed with 10% Na₂CO₃ and brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by reversed-phase preparative HPLC gave the titled compound. ESI+ MS: 453 [M+H]⁺.

15

EXAMPLE 65

5-Iodo-3-[[{(2-[[{(4-methoxyphenyl)sulfonyl]amino)ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide



Step A: Ethyl 3-(((2-((tert-butoxycarbonyl)amino)ethyl)amino)sulfonyl)-5-iodo-1-(phenylsulfonyl)-1H-indole-2-carboxylate

The product from Example 4 Step C (235 mg) was combined with
 5 Boc-ethylenediamine (74 μ L) and triethylamine (178 μ L) in 3 mL of dichloromethane and stirred at room temperature for 1 hour. The reaction was diluted with EtOAc and washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using EtOAc/hexane as mobile phase to give the titled compound. ESI+ MS: 678 $[\text{M}+\text{H}]^+$.

10

Step B: Ethyl 3-(((2-aminoethyl)amino)sulfonyl)-5-iodo-1-(phenylsulfonyl)-1H-indole-2-carboxylate hydrochloride

Through a solution of the product from Step A above (94 mg) in 6 mL of EtOAc at 0 $^\circ\text{C}$ was bubbled HCl gas for 2 minutes. The reaction was sealed, and
 15 stirring continued for 30 minutes. The solvent was removed *in vacuo* to give the titled compound. ESI+ MS: 579 $[\text{M}+\text{H}]^+$.

Step C: Ethyl 5-iodo-3-(((2-(((4-methoxyphenyl)sulfonyl)amino)ethyl)amino)sulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate

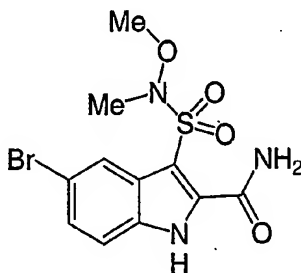
The product from Step B above (25 mg) was combined with 4-methoxybenzenesulfonyl chloride (74 μ L) and triethylamine (23 μ L) in 1 mL of dichloromethane and stirred at room temperature for 1 hour. The reaction was diluted with EtOAc, washed with saturated NaHCO_3 and brine. The solution was dried over Na_2SO_4 and concentrated *in vacuo* to give the titled compound. ESI+ MS: 678
 25 $[\text{M}+\text{H}]^+$.

Step D: 5-Iodo-3-([(2-([(4-methoxyphenyl)sulfonyl]amino)ethyl)amino]sulfonyl)-1H-indole-2-carboxamide

The product from Step C was dissolved in isopropanol, and cooled to 0 °C. Ammonia was bubbled through the solution for 2 minutes. The reaction was sealed and heated in a pressure vessel at 100 °C for 6 hours. After concentrating *in vacuo* the crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₈H₂₀IN₄O₆S₂ [M+H]⁺: 578.9863. Found 578.9865.

EXAMPLE 66

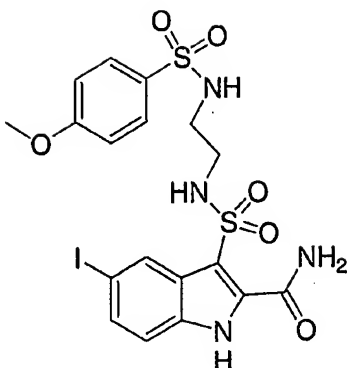
5-Bromo-3-{[methoxy(methyl)amino]sulfonyl}-1H-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate, and methylamine hydrochloride with *N*-methoxy-*N*-methylamine hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 362.13 [M+H]⁺.

EXAMPLE 67

5-Fluoro-3-([(2-([(4-methoxyphenyl)sulfonyl]amino)ethyl)(methyl)amino]sulfonyl)-1H-indole-2-carboxamide



Step A: Ethyl 3-(chlorosulfonyl)-5-fluoro-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

- Following the procedures described in Steps A-C of Example 1, replacing ethyl 5-chloro-1*H*-indole-2-carboxylate with ethyl 5-fluoro-1*H*-indole-2-carboxylate in Step A, the titled compound was obtained. ESI+ MS: 432 [M+H]⁺.

Step B: *tert*-Butyl 2-[[[(4-methoxyphenyl)sulfonyl]amino]ethyl(methyl)carbamate

- In 5 mL of dichloromethane, *tert*-butyl 2-aminoethyl(methyl)carbamate (127 mg), 4-methoxybenzenesulfonyl chloride (150mg) and triethylamine (101 μ L) were combined and stirred at room temperature for 1 hour and 15 minutes. The reaction was diluted with EtOAc and washed with sat. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 244 [MH-Boc]⁺.

Step C: 4-Methoxy-*N*-[2-(methylamino)ethyl]benzenesulfonamide Hydrochloride

- Through a solution of the product from Step B above (277 mg) in 10 mL of EtOAc at 0 °C was bubbled HCl gas for 2 minutes. The reaction was sealed, and stirring continued for 30 minutes. The solvent was removed *in vacuo* to give the titled compound. ESI+ MS: 245 [M+H]⁺.

Step D: Ethyl 5-fluoro-3-[[[(2-[[[(4-methoxyphenyl)sulfonyl]amino]ethyl(methyl)amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

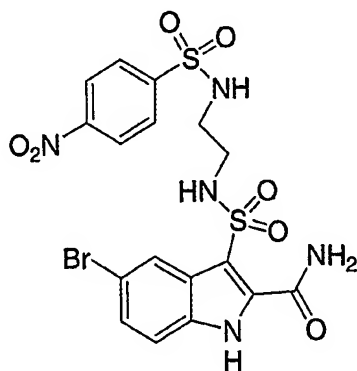
The product from Step A above (1 equivalent) was combined with the product from Step C above (1 equivalent) and triethylamine (3 equivalents) in dichloromethane and stirred at room temperature for 1.5 hours. The reaction was diluted with EtOAc, washed with saturated NaHCO₃ and brine and dried over Na₂SO₄. Concentrating *in vacuo* gave the titled compound. ESI+ MS: 640 [MH-CH₃]⁺.

Step E: 5-Fluoro-3-([(2-([(4-methoxyphenyl)sulfonyl]amino)ethyl)(methyl)amino]sulfonyl)-1*H*-indole-2-carboxamide

The product from Step D above was dissolved in isopropanol, and cooled to 0 °C. Ammonia was bubbled through the solution for 2 minutes. The reaction was sealed and heated in a pressure vessel at 100 °C for 3 hours. After concentrating *in vacuo* the crude product was purified by reversed-phase preparative HPLC to give the titled compound. HRMS (ES) exact mass calculated for C₁₉H₂₂FN₄O₆S₂ [M+H]⁺:485.0960. Found 485.0955.

EXAMPLE 68

5-Bromo-3-([(2-([(4-nitrophenyl)sulfonyl]amino)ethyl)amino]sulfonyl)-1*H*-indole-2-carboxamide



Step A: Ethyl 5-bromo-3-([(2-([(4-nitrophenyl)sulfonyl]amino)ethyl)amino]sulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

The product from Example 89 Step A, as described hereinbelow, (1 equivalent) was stirred in dichloromethane with 4-nitrophenylsulfonyl chloride (1

equivalent) and triethylamine (3 equivalents) for 45 minutes at room temperature. The solvent was removed under a stream of nitrogen to give the titled compound. ESI+ MS: 715 [M+H]⁺.

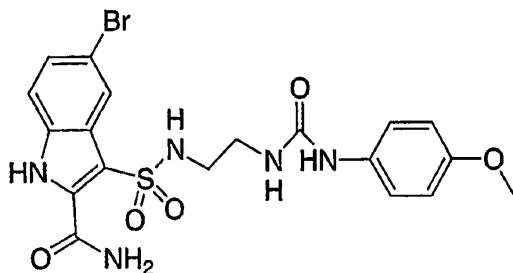
5 Step B: 5-Bromo-3-({[2-({[(4-nitrophenyl)sulfonyl]amino}ethyl)amino]sulfonyl})-1*H*-indole-2-carboxamide

The product from Step A was dissolved in isopropanol, and cooled to 0 °C. Ammonia was bubbled through the solution for 2 minutes. The reaction was sealed and heated in a pressure vessel at 100 °C for 3.5 hours. After concentrating *in vacuo* the crude product was purified by reversed-phase preparative HPLC to give the titled compound. HRMS (ES) exact mass calculated for C₁₇H₁₇BrN₅O₇S₂ [M+H]⁺: 545.9747. Found 545.9725.

EXAMPLE 69

15

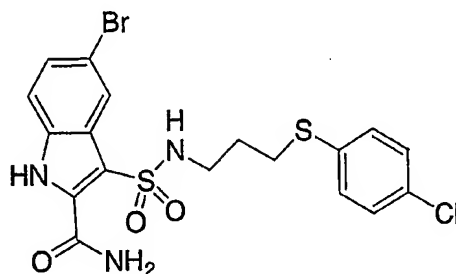
5-Bromo-3-({[2-({[(4-methoxyphenyl)amino]carbonyl}amino)ethyl]amino}sulfonyl)-1*H*-indole-2-carboxamide



The product from Example 63 (50 mg) was combined with 4-methoxyphenyl isocyanate (21 mg) and triethylamine (58 µL) in 2 mL of dichloromethane and stirred at room temperature for 3 hours. An additional 18 µL of the isocyanate were added and the reaction stirred for 3 hours more, then diluted with EtOAc and washed with saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified by preparative reversed-phase HPLC followed by trituration with Et₂O/hexane to give the titled product. ESI+ MS: 510 [M+H]⁺

EXAMPLE 70

5-Bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino)sulfonyl]-1H-indole-2-carboxamide



Step A: 3-[(*tert*-Butoxycarbonyl)amino]propyl methanesulfonate

To a stirring solution of *tert*-butyl 3-hydroxypropylcarbamate (431 mg) at 0 °C in dichloromethane, triethylamine (686 µL) was added, followed by methanesulfonyl chloride (209 µL). The reaction was stirred for 15 minutes, then allowed to warm to room temperature and stir for 1 hour more. Additional triethylamine (686 µL) and methanesulfonyl chloride (209 µL) were added. One hour later the reaction was diluted with EtOAc and washed with saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 259 [M+H]⁺.

Step B: *tert*-Butyl 3-[(4-chlorophenyl)thio]propylcarbamate

A solution of 4-chlorothiophenol (91 mg) in 6 mL of DMF was cooled to 0 °C under N₂. Sodium hydride (60%, 30 mg) was added and the reaction stirred for 30 minutes. The product from Step A above in 3 mL of DMF was added and the reaction allowed to warm to room temperature while stirring overnight. This was diluted with EtOAc, washed with saturated NaHCO₃ and brine and dried over Na₂SO₄. Concentrating *in vacuo* gave the titled compound. ESI+ MS: 202 [MH-Boc]⁺.

Step C: 3-[(4-Chlorophenyl)thio]propan-1-amine hydrochloride

Through a solution of the product from Step B above (50 mg) in 10 mL of EtOAc at 0 °C was bubbled HCl gas for 2 minutes. The reaction was sealed, and

stirring continued for 30 minutes. The solvent was removed *in vacuo* to give the titled compound. ESI+ MS: 202 [M+H]⁺.

5 Step D: Ethyl 5-bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino)sulfonyl]-1-(phenylsulfonyl)-1 *H*-indole-2-carboxylate

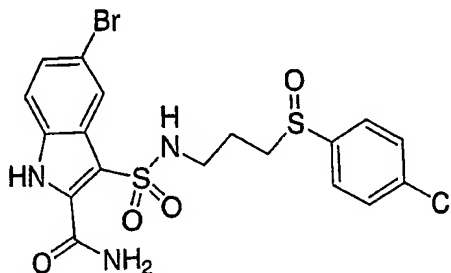
10 The product from Step C (16 mg) was combined and stirred with the product from Example 3 Step A (35 mg) and triethylamine (29 μ L) in 3 mL of dichloromethane at room temperature for 1.5 hours. The reaction was diluted with EtOAc and washed with saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 672.8 [M+H]⁺.

15 Step E: 5-Bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino)sulfonyl]-1 *H*-indole-2-carboxamide

20 The product from Step D was dissolved in 5 mL isopropanol, and cooled to 0 °C. Ammonia was bubbled through the solution for 2 minutes. The reaction was sealed and heated in a pressure vessel at 100 °C overnight. After concentrating *in vacuo* the crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₈H₁₈BrClN₃O₃S₂ [M+H]⁺: 501.9656. Found 501.9664.

EXAMPLE 71

25 5-Bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino)sulfonyl]-1 *H*-indole-2-carboxamide



Step A: *tert*-Butyl 3-[(4-chlorophenyl)sulfinyl]propylcarbamate

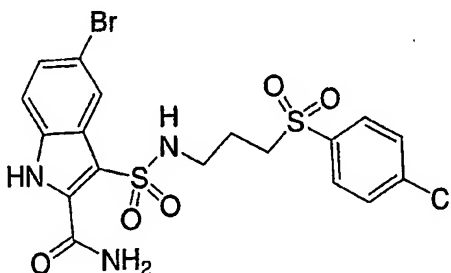
The product from Example 70 Step B (70 mg) was stirred in 2 mL of dichloromethane with 3-chloroperoxybenzoic acid (MCPBA) (40 mg) for 1 hour at 0 °C. An additional 5 mg of MCPBA was added and the reaction stirred 30 minutes more, then diluted with EtOAc and washed with saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 218 [MH-Boc]⁺.

Step B: 5-Bromo-3-[(3-[(4-chlorophenyl)thio]propyl)amino)sulfonyl]-1 *H*-indole-2-carboxamide

Following the procedures of Example 70 Steps C through E, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₈H₁₈BrClN₃O₄S₂ [M]⁺: 517.9605. Found 517.9576.

EXAMPLE 72

5-Bromo-3-[(3-[(4-chlorophenyl)sulfonyl]propyl)amino)sulfonyl]-1 *H*-indole-2-carboxamide



Step A: *tert*-Butyl 3-[(4-chlorophenyl)sulfonyl]propylcarbamate

The product from Example 70 Step B (70 mg) was stirred in 2 mL of dichloromethane with MCPBA (88 mg) for 1 hour at 0 °C. An additional 20 mg of MCPBA was added and the reaction stirred 30 minutes more then diluted with EtOAc and washed with saturated NaHCO₃ and brine. The solution was dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 234 [MH-Boc]⁺.

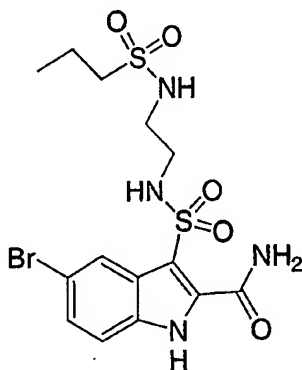
Step B: 5-Bromo-3-[(3-[(4-chlorophenyl)sulfonyl]propyl)amino)sulfonyl]-1*H*-indole-2-carboxamide

Following the procedures of Example 70 Steps C through E, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{18}H_{18}BrClN_3O_5S_2$ $[M]^+$: 533.9555. Found 533.9549.

5

EXAMPLE 73

5-Bromo-3-[[{(propylsulfonylamino)ethylamino)sulfonyl]-1*H*-indole-2-carboxamide
hydrochloride



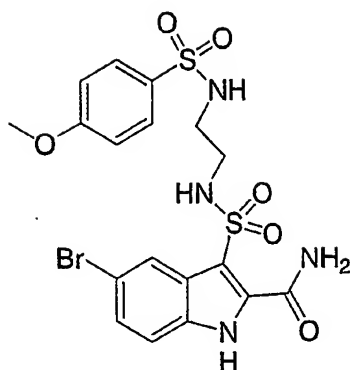
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Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with propanesulfonyl chloride, the titled compound was prepared. ESI+ MS: 467 $[M+H]^+$.

15

EXAMPLE 74

5-Bromo-3-[[{(2-[[{(4-methoxyphenyl)sulfonyl]amino}ethyl)amino]sulfonyl)-1*H*-
indole-2-carboxamide

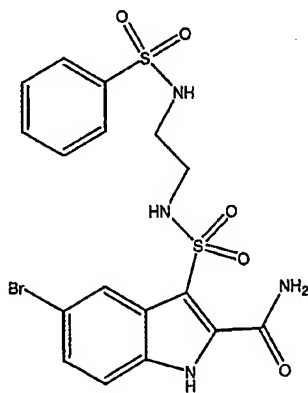


Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 4-methoxybenzenesulfonyl chloride, the titled compound was prepared. ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 8.37 (s, 1H), 8.19 (s, 1H), 8.09 (d, $J=1.9$ Hz, 1H), 7.58 (d, $J=8.9$ Hz, 2H), 7.50 (d, $J=8$ Hz, 1H), 7.46 (dd, $J=1.9$, 8.8 Hz, 1H), 7.19 (br s, 3H), 7.04 (d, $J=8.9$ Hz, 2H), 3.84 (s, 3H), 2.80 (t, $J=7$ Hz, 2H), 2.68 (t, $J=7$ Hz, 2H) ppm. ESI+ MS: 531 $[\text{M}+\text{H}]^+$.

EXAMPLE 75

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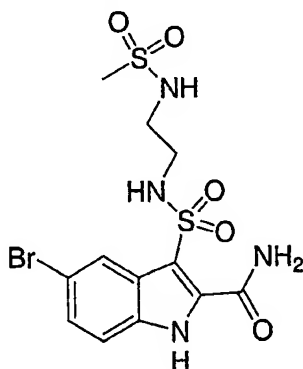
5-Bromo-3-[(2-[(phenylsulfonyl)amino]ethyl)amino)sulfonyl]-1H-indole-2-carboxamide



Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with benzenesulfonyl chloride, the titled compound was prepared. ESI+ MS: 501 $[\text{M}+\text{H}]^+$.

EXAMPLE 76

5-Bromo-3-[(2-[(methanesulfonyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide



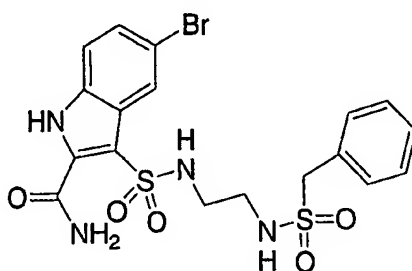
5

Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with methanesulfonyl chloride, the titled compound was prepared. ESI+ MS: 439 [M+H]⁺.

10

EXAMPLE 77

3-[(2-[(Benzylsulfonyl)amino]ethyl)amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide

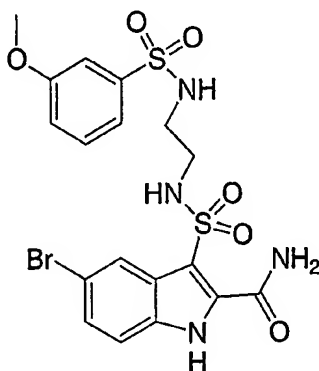


15

Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with benzylsulfonyl chloride, the titled compound was prepared. ESI+ MS: 515 [M+H]⁺.

EXAMPLE 78

5-Bromo-3-[[[2-[[[(3-methoxyphenyl)sulfonyl]amino]ethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide]



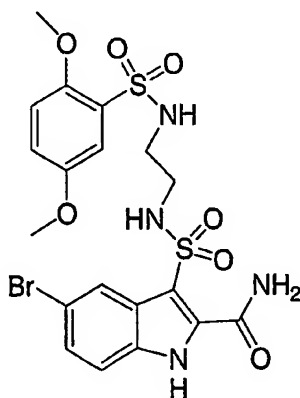
5

Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 3-methoxybenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 531 [M+H]⁺.

10

EXAMPLE 79

5-Bromo-3-[[[2-[[[(2,5-dimethoxyphenyl)sulfonyl]amino]ethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide]



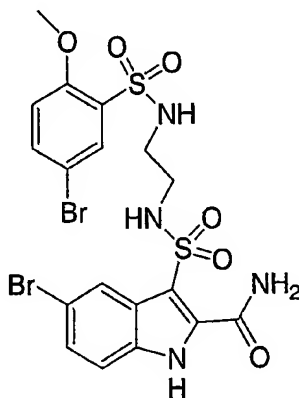
15

Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 2,5-dimethoxybenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 561 [M+H]⁺.

5

EXAMPLE 80

5-Bromo-3-([(2-[(5-bromo-2-methoxyphenyl)sulfonyl]amino)ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide



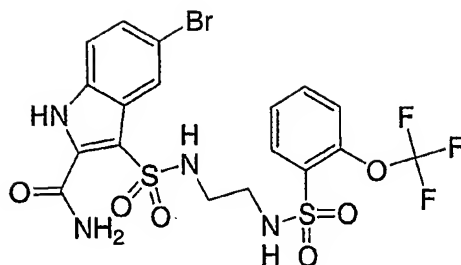
10

Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 5-bromo-2-methoxybenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 610.9 [M+H]⁺.

15

EXAMPLE 81

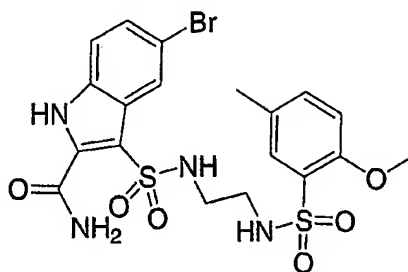
5-Bromo-3-([(2-([2-(trifluoromethoxy)phenyl]sulfonyl)amino)ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide



Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 2-trifluoromethoxybenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled
 5 compound. ESI+ MS: 585 [M+H]⁺.

EXAMPLE 82

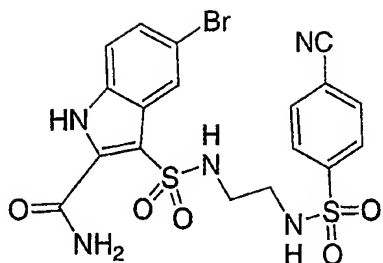
5-Bromo-3-{[(2-{[(2-methoxy-5-methylphenyl)sulfonyl]amino}ethyl)amino]
 10 sulfonyl]-1*H*-indole-2-carboxamide



Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 2-methoxy-5-methylbenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled
 15 compound. HRMS (ES) exact mass calculated for C₁₉H₂₂BrN₄O₆S₂ [M]⁺: 545.0159. Found 545.0174.

EXAMPLE 83

20 5-Bromo-3-{[(2-{[(4-cyanophenyl)sulfonyl]amino}ethyl)amino]sulfonyl]-1*H*-indole-
2-carboxamide

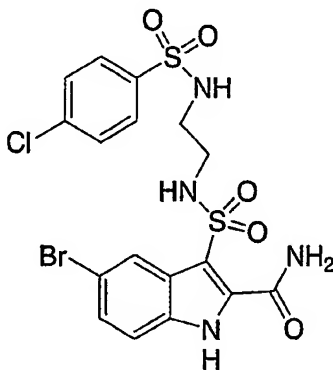


Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 4-cyanobenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound.

- 5 HRMS (ES) exact mass calculated for $C_{18}H_{17}BrN_5O_5S_2$ $[M+H]^+$: 525.9849. Found 525.9839.

EXAMPLE 84

- 10 5-Bromo-3-[[[2-[[[4-chlorophenyl)sulfonyl]amino]ethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide

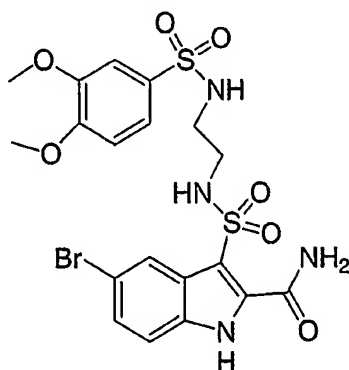


Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 4-chlorobenenesulfonyl chloride, the titled compound

- 15 was prepared. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{17}H_{17}ClBrN_5O_5S_2$ $[M+H]^+$: 534.9507. Found 534.9513.

EXAMPLE 85

5-Bromo-3-[[[2-[[[(3,4-dimethoxyphenyl)sulfonyl]amino]ethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide]



5

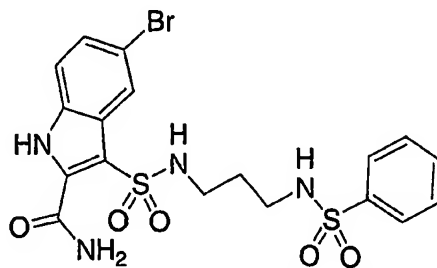
Following the procedure described in Example 64, except replacing the ethanesulfonyl chloride with 3,4-dimethoxybenenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{19}H_{22}BrN_4O_7S_2$ $[M+H]^+$:

10 561.0131. Found 561.0108.

EXAMPLE 86

5-Bromo-3-[[[3-[(phenylsulfonyl)amino]propyl]amino]sulfonyl]-1*H*-indole-2-carboxamide

15



Step A:

Ethyl 5-bromo-3-[[[3-[(tert-butoxycarbonyl)amino]propyl]amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

To a solution of 200 mg ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate (Example 3, Step A) in 2 mL dichloromethane, triethylamine was added (165 μ L), followed by *tert*-butyl 3-aminopropylcarbamate (76 mg). The reaction was stirred for 2 hours at room temperature. The reaction was diluted with EtOAc, washed with saturated NaHCO₃ and brine and dried over Na₂SO₄. The crude product was purified by flash chromatography on silica using EtOAc:hexane (1:3) as mobile phase to give the titled compound. ESI+ MS: 644 [M+H]⁺.

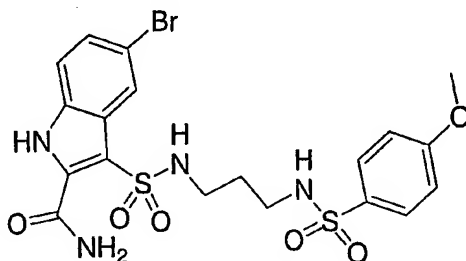
10 Step B: Ethyl 3-[[[(3-aminopropyl)amino]sulfonyl]-5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate hydrochloride
Through a solution of the product from Step A above (60 mg) in 10 mL of EtOAc at 0 °C was bubbled HCl gas for 2 minutes. The reaction was sealed, and stirring continued for 30 minutes. The solvent was removed *in vacuo* to give the titled
15 compound. ESI+ MS: 544 [M+H]⁺.

Step C: Ethyl 5-bromo-1-(phenylsulfonyl)-3-[[[(3-[(phenylsulfonyl)amino]propyl)amino]sulfonyl]-1*H*-indole-2-carboxylate
The material from Step B above (20 mg) was dissolved in 1 mL of
20 dichloromethane. Triethylamine (19 μ L) was added, followed by benzenesulfonyl chloride (5 μ L), and the reaction stirred for 45 minutes at room temperature. The solvent removed under a stream of nitrogen. ESI+ MS: 684 [M+H]⁺.

Step D: Ethyl 5-bromo-3-[[[(3-[(*tert*-butoxycarbonyl)amino]propyl)amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate
The product from Step D was dissolved in 5 mL isopropanol, and cooled to 0 °C. Ammonia was bubbled through the solution for 2 minutes. The reaction was sealed and heated in a pressure vessel at 100 °C for 7 hours. After concentrating under a stream of nitrogen, the crude product was purified by reversed-
30 phase preparative HPLC to give the titled compound. HRMS (ES) exact mass calculated for C₁₈H₂₀BrN₄O₅S₂ [M+H]⁺: 515.0053. Found 515.0043.

EXAMPLE 87

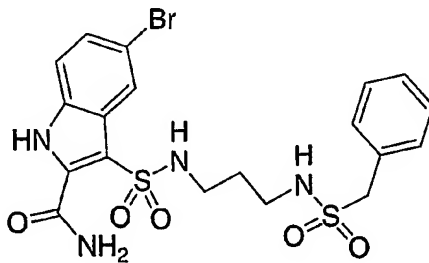
5-Bromo-3-[[[3-[[[4-methoxyphenyl)sulfonyl]amino]propyl]amino]sulfonyl]-1*H*-indole-2-carboxamide



Following the procedure described in Example 86 Steps C and D, except replacing the benzenesulfonyl chloride with 4-methoxybenzenesulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{19}H_{22}BrN_4O_6S_2$ $[M+H]^+$: 545.0159. Found 545.0138

EXAMPLE 88

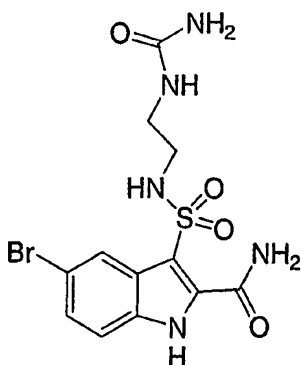
3-[[[3-[(Benzy)sulfonyl]amino]propyl]amino]sulfonyl]-5-bromo-1*H*-indole-2-carboxamide



Following the procedure described in Example 86 Steps C and D, except replacing the benzenesulfonyl chloride with benzylsulfonyl chloride, the titled compound was prepared. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for $C_{19}H_{22}BrN_4O_5S_2$ $[M]^+$: 529.0210. Found 529.0185.

EXAMPLE 89

3-[[[2-[(Aminocarbonyl)amino]ethyl]amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide



5

Step A: Ethyl 3-[[[2-(2-aminoethyl)amino]sulfonyl]-5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate hydrochloride

A solution of the product from Example 62 Step A, was dissolved in EtOAc and cooled to 0 °C. HCl gas was bubbled through for 3 minutes. The reaction was stirred for 1 hour, then was concentrated *in vacuo* to give the titled compound.

10

Step B: Ethyl 5-bromo-3-[[[2-[[[4-methoxyphenyl]amino]carbonyl]amino]ethyl]amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

A solution of the material from Step A above (25 mg) was dissolved in 1 mL of THF and cooled to 0 °C. Triethylamine (25 µL) was added, followed by 4 mg of triphosgene. The reaction stirred for 5 minutes at 0 °C, then 5 minutes at room temperature and then was recooled to 0 °C and stirred for 5 minutes more. A solution of 4-methoxyaniline in 1 mL of THF was added slowly. The reaction was stirred for 40 minutes, diluted with EtOAc and washed with 10% citric acid solution, saturated NaHCO₃ and brine. The solution was dried (Na₂SO₄) and concentrated *in vacuo* to give the titled product.

15

20

Step C: 3-[[[2-[(Aminocarbonyl)amino]ethyl]amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide

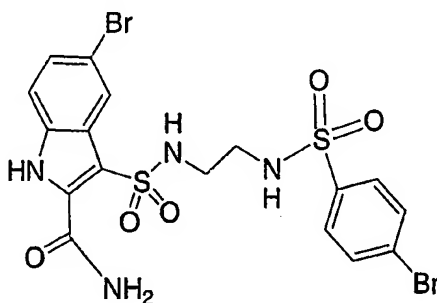
The product from Step B above (26 mg) was dissolved in isopropanol, and cooled to 0 °C. Ammonia was bubbled through the solution for 2 minutes. The

25

reaction was sealed and heated in a pressure vessel at 80 °C for 1 hour. After concentrating *in vacuo* the crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₂H₁₅BrN₅O₄S [M+H]⁺:
 5 404.2445. Found 404.0026.

EXAMPLE 90

5-Bromo-3-{{(2-{{[(4-bromophenyl)sulfonyl]amino}ethyl]amino}sulfonyl)-1*H*-indole-
 10 2-carboxamide



Step A: Ethyl 5-bromo-3-{{(2-{{[(4-bromophenyl)sulfonyl]amino}ethyl]amino}sulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

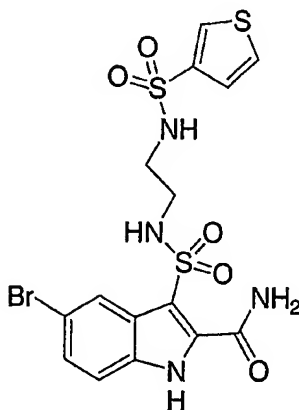
A solution of the product from Example 89 Step A, was combined with
 15 4-bromobenzenesulfonyl chloride and triethylamine, and stirred at room temperature for 35 minutes. The solvent was removed with a stream of nitrogen to give the titled compound. ESI+ MS: 750 [M+H]⁺.

Step B: 5-Bromo-3-{{(2-{{[(4-bromophenyl)sulfonyl]amino}ethyl]amino}sulfonyl)-1*H*-indole-2-carboxamide

The procedure from Example 89, Step C was followed, except substituting the material from Step A and increasing the heating time to 2 hours. The crude product was recrystallized from hot acetonitrile to give the titled compound. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 581
 25 [M+H]⁺.

EXAMPLE 91

5-Bromo-3-[[{2-[(thien-3-ylsulfonyl)amino]ethyl}amino)sulfonyl]-1*H*-indole-2-carboxamide



Step A: Ethyl 5-bromo-1-(phenylsulfonyl)-3-[[{2-[(thien-3-ylsulfonyl)amino]ethyl}amino)sulfonyl]-1*H*-indole-2-carboxylate

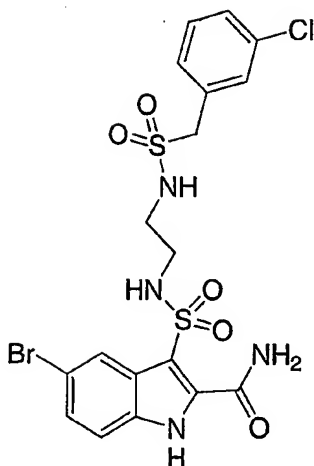
Following the procedure described in Example 90 Step A, except replacing the 4-bromobenzenesulfonyl chloride with 3-thiophenesulfonyl chloride, the titled compound was obtained. ESI+ MS: 676 [M+H]⁺.

Step B: 5-Bromo-3-[[{2-[(thien-3-ylsulfonyl)amino]ethyl}amino)sulfonyl]-1*H*-indole-2-carboxamide

The procedure of example 89 Step C was followed, except substituting the material from Step A and increasing the heating time to 3 hours. The crude product was recrystallized from hot acetonitrile to give the titled compound. HRMS (ES) exact mass calculated for C₁₅H₁₆BrN₄O₅S₃ [M+1]⁺: 506.9388. Found 506.9458.

EXAMPLE 92

5-Bromo-3-[[{2-[[{(3-chlorobenzyl)sulfonyl]amino}ethyl]amino)sulfonyl]-1*H*-indole-2-carboxamide



Step A: Ethyl 5-bromo-3-((2-((3-chlorobenzyl)sulfonyl)amino)ethyl)amino]sulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate

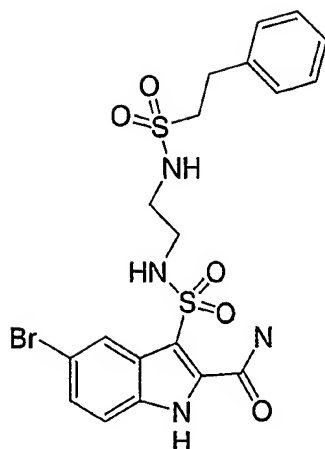
Following the procedure described in Example 90 Step A, except
 5 replacing the 4-bromobenzenesulfonyl chloride with *m*-chlorobenzylsulfonyl chloride, the titled compound was obtained. ESI+ MS: 720 [M+H]⁺.

Step B: 5-Bromo-3-((2-((3-chlorobenzyl)sulfonyl)amino)ethyl)amino]sulfonyl)-1H-indole-2-carboxamid

10 The procedure of Example 89 Step C was followed, except substituting the material from Step A and increasing the heating time to 3 hours. The crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₈H₁₉ClBrN₄O₅S₂ [M+H]⁺: 548.9663. Found
 15 548.9666.

EXAMPLE 93

5-Bromo-3-((2-((2-phenylethyl)sulfonyl)amino)ethyl)amino]sulfonyl)-1H-indole-
 20 2-carboxamide



Step A: Ethyl 5-bromo-3-({[2-({[2-phenylethyl)sulfonyl]amino}ethyl)amino]sulfonyl}-1-(phenylsulfonyl)-1H-indole-2-carboxylate

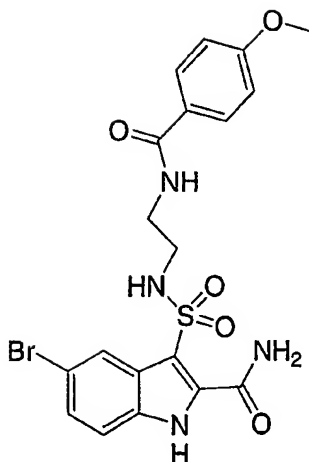
Following the procedure described in Example 90 Step A, except replacing the 4-bromobenzenesulfonyl chloride with phenethylsulfonyl chloride, the titled compound was obtained. ESI+ MS: 698 [M+H]⁺.

Step B: 5-Bromo-3-({[2-({[2-phenylethyl)sulfonyl]amino}ethyl)amino]sulfonyl}-1H-indole-2-carboxamide

The procedure of Example 89 Step C was followed, except substituting the material from Step A and increasing the heating time to 3 hours. The crude product was purified on the Water HPLC system to give the titled compound. Proton NMR for the product was consistent with the titled compound. HRMS (ES) exact mass calculated for C₁₉H₂₂BrN₄O₅S₂ [M+H]⁺: 529.0137. Found 529.0210.

EXAMPLE 94

5-Bromo-3-({[2-({[4-methoxybenzoyl]amino}ethyl)amino]sulfonyl}-1H-indole-2-carboxamide



Step A: Ethyl 5-bromo-3-[(2-[(4-methoxybenzoyl)amino]ethyl)amino)sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

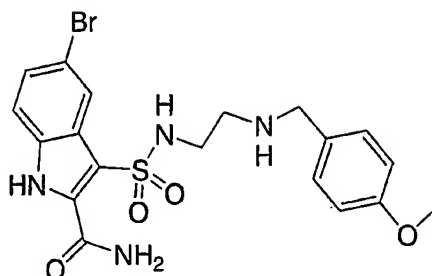
- The product from Example 89, Step A was combined with 1.1 equivalents of 4-methoxybenzoyl chloride and 3.0 equivalents of triethylamine in dichloromethane. The reaction was stirred for 1.5 hours at room temperature and the solvent was removed under a stream of nitrogen to give the titled compound. ESI+ MS: 664 [M+H]⁺.

Step B: 5-Bromo-3-[(2-[(2-phenylethyl)sulfonyl]amino)ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide

- The procedure of Example 89 Step C was followed, except substituting the material from Step A and increasing the heating time to 3 hours. The crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 495 [M+H]⁺.

EXAMPLE 95

5-Bromo-3-[(2-[(4-methoxybenzyl)amino]ethyl)amino)sulfonyl]-1*H*-indole-2-carboxamide



Step A: Ethyl 5-bromo-3-[(2-[(4-methoxybenzyl)amino]ethyl)amino)sulfonyl]-1-(phenylsulfonyl)-1H-indole-2-carboxylate

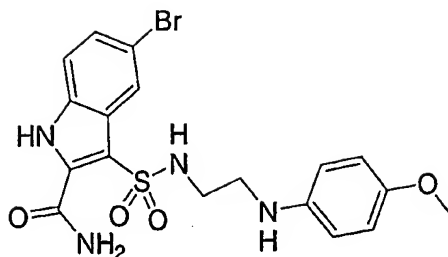
The product from Example 89, Step A was combined with 1.2 equivalents of 4-methoxybenzaldehyde and 1.5 equivalent of sodium triacetoxyborohydride in dichloroethane. The reaction was stirred for 1.5 hours at room temperature, was diluted with EtOAc and washed with sat. NaHCO₃ and brine. The solution was dried with Na₂SO₄ and concentrated *in vacuo* to give the titled compound. ESI+ MS: 651 [M+H]⁺.

Step B: 5-Bromo-3-[(2-[(4-methoxybenzyl)amino]ethyl)amino)sulfonyl]-1H-indole-2-carboxamide

The procedure of Example 89 Step C was followed, except substituting the material from Step A and increasing the heating time to 3 hours. The crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 481 [M+H]⁺.

EXAMPLE 96

5-Bromo-3-[(2-[(4-methoxyphenyl)amino]ethyl)amino)sulfonyl]-1H-indole-2-carboxamide



Step A: Ethyl *tert*-butyl 2-[(4-methoxyphenyl)amino]ethylcarbamate

A solution of *tert*-butyl 2-oxoethylcarbamate (153 mg), 4-methoxyaniline (118 mg), sodium triacetoxyborohydride (306 mg) and acetic acid
 5 (0.275 mL) were stirred in 5 mL dichloroethane at room temperature. To this a small amount of powdered 4A sieves were added and the reaction stirred for 1.5 hours. The reaction was diluted with EtOAc and washed with sat. NaHCO₃ and brine, dried Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica using EtOAc/hexane (1:2) to obtain the titled compound.
 10 ESI+ MS: 267 [M+H]⁺.

Step B: *N*-(4-Methoxyphenyl)ethane-1,2-diamine dihydrochloride

Through a solution of the product from Step A (85 mg) in 3 mL of EtOAc at 0 °C was bubbled HCl gas for 2 minutes. The reaction was sealed, and
 15 stirring continued for 30 minutes. The solvent was removed *in vacuo* to give the titled compound.

Step C: Ethyl 5-bromo-3-[(2-[(4-methoxyphenyl)amino]ethyl)amino]sulfonyl]-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

The material from Step B (59 mg) was combined with the product of Example 3 Step A (147 mg) and triethylamine (121 µL) in 3 mL of dichloromethane, and stirred at room temperature for 4 hours. The reaction was diluted with EtOAc and washed with sat. NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give the titled compound.
 20

Step D: 5-Bromo-3-[(2-[(4-methoxyphenyl)amino]ethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide

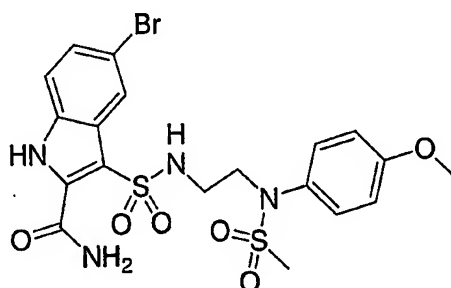
The procedure of Example 89 Step C was followed, except substituting the material from Step C (26 mg) and increasing the heating time to 3 hours. The
 25

crude purified by reversed-phase preparative HPLC to give the titled compound.
Proton NMR for the product was consistent with the titled compound. ESI+ MS: 467
[M+H]⁺.

5

EXAMPLE 97

5-Bromo-3-[(2-[(4-methoxyphenyl)(methylsulfonyl)amino]ethyl)amino)sulfonyl]-
1H-indole-2-carboxamide



10 Step A: Ethyl 5-bromo-3-[(2-[(4-methoxyphenyl)(methylsulfonyl)amino]
ethyl)amino)sulfonyl]-1-(phenylsulfonyl)-1 H-indole-2-carboxylate

The material from Example 96, Step C was combined with
methanesulfonyl chloride (1.1 equivalents) and triethylamine (3 equivalents) in
dichloromethane, and stirred for for one hour at room temperature. The reaction was
15 diluted with EtOAc, washed with sat NaHCO₃ and brine, dried over Na₂SO₄ and
concentrated *in vacuo* to obtain the titled compound. ESI+ MS: 714 [M+H]⁺.

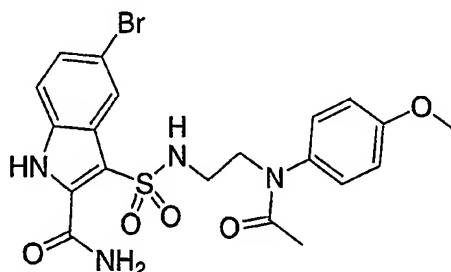
Step B: 5-Bromo-3-[(2-[(4-methoxyphenyl)(methylsulfonyl)amino]ethyl)
amino)sulfonyl]-1H-indole-2-carboxamide

20 The procedure of Example 89 Step C was followed, except substituting
the material from Step A and increasing the heating time to 16 hours. The crude
product was purified by reversed-phase preparative HPLC to give the titled
compound. Proton NMR for the product was consistent with the titled compound.
ESI+ MS: 545 [M+H]⁺.

25

EXAMPLE 98

3-[(2-[Acetyl(4-methoxyphenyl)amino]ethyl)amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide



5

Step A: Ethyl 3-[(2-[acetyl(4-methoxyphenyl)amino]ethyl)amino)sulfonyl]-5-bromo-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate

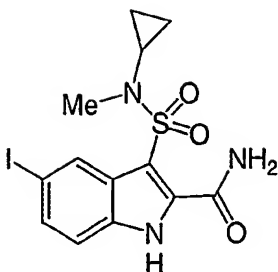
The material from Example 96, Step C was combined with acetyl chloride (1.1 equivalents) and triethylamine (3 equivalents) in dichloromethane and stirred for two hours at room temperature. The reaction was diluted with EtOAc, washed with sat NaHCO₃ and brine, dried over Na₂SO₄ and concentrated *in vacuo* to obtain the titled compound. ESI+ MS: 678 [M+H]⁺.

Step B: 3-[(2-[Acetyl(4-methoxyphenyl)amino]ethyl)amino)sulfonyl]-5-bromo-1*H*-indole-2-carboxamide

The procedure of Example 89 Step C was followed, except substituting the material from Step A and increasing the heating time to 16 hours. The crude product was purified by reversed-phase preparative HPLC to give the titled compound. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 509 [M+H]⁺.

EXAMPLE 99

5-Iodo-3-{[cyclopropyl(methyl)amino]sulfonyl}-1*H*-indole-2-carboxamide

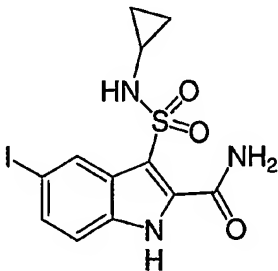


Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with *N*-cyclopropyl-*N*-methylammonium oxylate, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 420.16 [M+H]⁺.

EXAMPLE 100

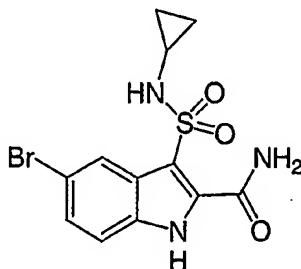
10

5-Iodo-3-[(cyclopropylamino)sulfonyl]-1*H*-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with cyclopropylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 406.13 [M+H]⁺.

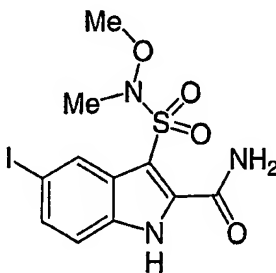
EXAMPLE 101

5-Bromo-3-[(cyclopropylamino)sulfonyl]-1H-indole-2-carboxamide

5 Following the procedures described in Steps D and E of Example 1,
replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-
carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-
carboxylate, and methylamine hydrochloride with cyclopropylamine, the title
10 compound was obtained. Proton NMR for the product was consistent with the titled
compound. ESI+ MS: 458.16 [M+H]⁺.

EXAMPLE 102

15 5-Iodo-3-[[methoxy(methyl)amino]sulfonyl]-1H-indole-2-
carboxamide



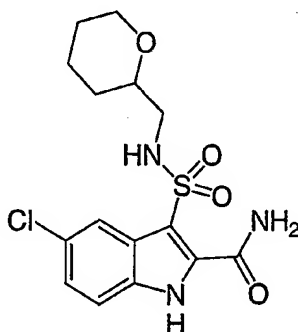
20 Following the procedures described in Steps D and E of Example 1,
replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-
carboxylate with ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-
carboxylate, and methylamine hydrochloride with N-methoxy-N-methylamine

hydrochloride, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 410.11 [M+H]⁺.

EXAMPLE 103

5

(±)-5-Chloro-3-[[[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide

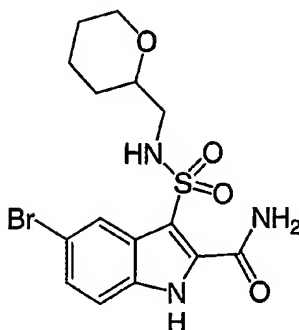


Following the procedures described in Steps D and E of Example 1,
10 replacing in Step D methylamine hydrochloride with (±)-1-tetrahydro-2*H*-pyran-2-ylmethanamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 371.98 [M+H]⁺.

EXAMPLE 104

15

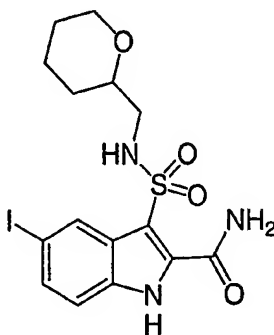
(±)-5-Bromo-3-[[[(tetrahydro-2*H*-pyran-2-ylmethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide



- Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with (±)-1-tetrahydro-2*H*-pyran-2-ylmethanamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 415.93 [M+H]⁺.

EXAMPLE 105

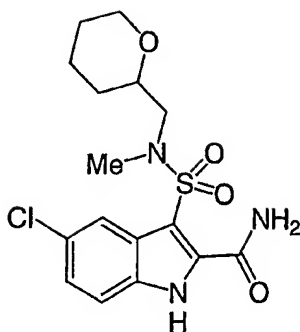
- (±)-5-Iodo-3-[[tetrahydro-2*H*-pyran-2-ylmethyl]amino]sulfonyl]-1*H*-indole-2-carboxamide
-



- Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with (±)-1-tetrahydro-2*H*-pyran-2-ylmethanamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 463.95 [M+H]⁺.

- EXAMPLE 106

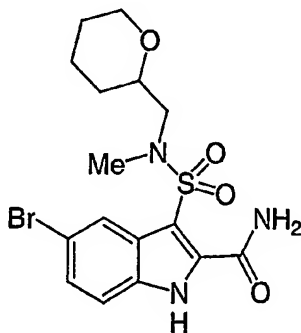
(±)-5-Chloro-3-[[methyl(tetrahydro-2*H*-pyran-2-ylmethyl)amino]sulfonyl]-1*H*-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D methylamine hydrochloride with (\pm)-*N*-(1-tetrahydro-2*H*-pyran-2-ylmethyl)-*N*-methylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 386.01 [M+H]⁺.

EXAMPLE 107

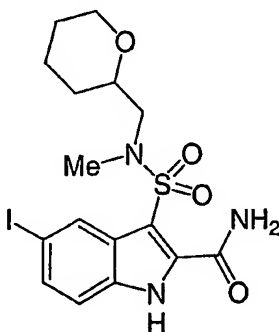
(\pm)-5-Bromo-3-{[methyl(tetrahydro-2*H*-pyran-2-ylmethyl)amino]sulfonyl}-1*H*-indole-2-carboxamide



Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate with ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1*H*-indole-2-carboxylate, and methylamine hydrochloride with (\pm)-*N*-(1-tetrahydro-2*H*-pyran-2-ylmethyl)-*N*-methylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 429.96 [M+H]⁺.

EXAMPLE 108

(±)-5-Iodo-3-{[methyl(tetrahydro-2H-pyran-2-ylmethyl)amino]sulfonyl}-1H-indole-2-carboxamide



5

Following the procedures described in Steps D and E of Example 1, replacing in Step D ethyl 5-chloro-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate with ethyl 5-iodo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate, and methylamine hydrochloride with (±)-N-(1-tetrahydro-2H-pyran-2-ylmethyl)-N-methylamine, the title compound was obtained. Proton NMR for the product was consistent with the titled compound. ESI+ MS: 477.99 [M+H]⁺.

10

EXAMPLE 109

15 5-Bromo-3-([2-(tert-butylthio)ethyl]amino)sulfonyl)-1-H-indole-2-carboxamide

To an 8 mL vial was placed ethyl 5-bromo-3-(chlorosulfonyl)-1-(phenylsulfonyl)-1H-indole-2-carboxylate (50 mg, 0.099 mmol), PS-NMM (58 mg, 0.216 mmol, 3.72 mmol/g), PS-DMAP (37 mg, 0.05 mmol, 1.48 mmol/g) and DCM. Then, 2-(tert-butylthio)ethanamine (15 µL, 0.08 mmol) was added, and the vial placed on a GlasCol orbital rotator for 16 hours. After this time, PS-trisamine resin (75 mg, 0.108 mmol, 1.44 mmol/g) was added to the vial to scavenge excess sulfonyl chloride.

20

Three hours later, the vial's contents were filtered through an Applied Separations filter tube, washed with DCM (3 x 3 mL) and concentrated in an HTII-12 Genevac unit to afford an orange oil. This material was then dissolved in 2 M NH₃/EtOH, sealed in a scintillation vial and heated to 90 degrees on a J-KEM heater/shaker block for 3 hours. The vial was then dried in an HTII-12 Genevac unit

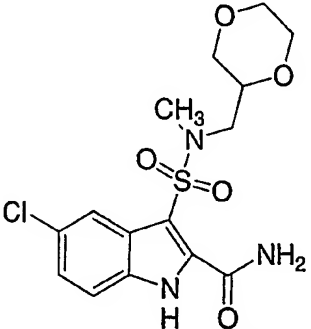
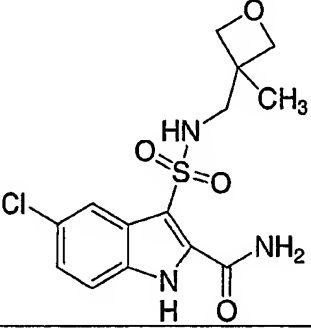
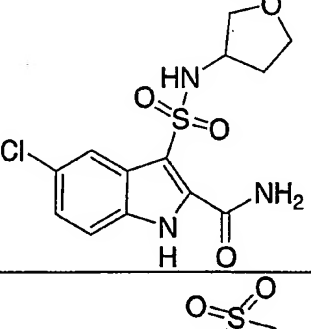
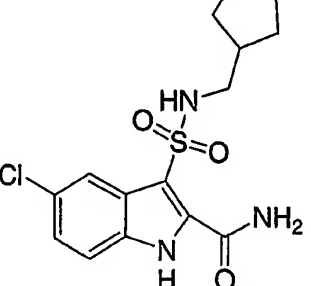
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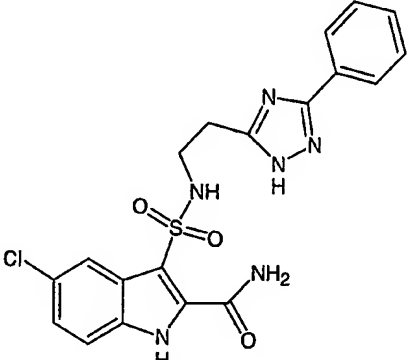
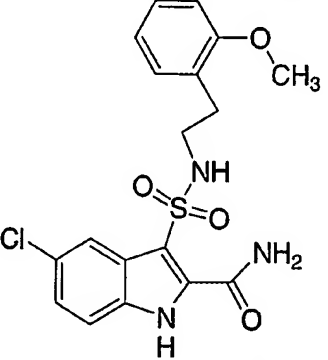
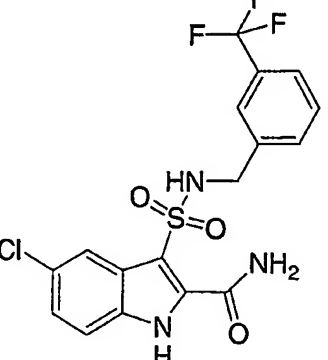
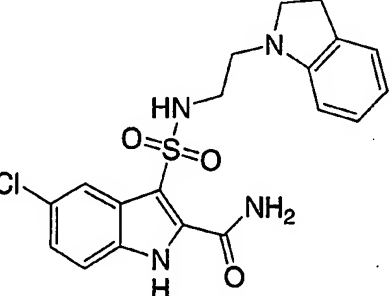
to afford an yellow oil. This material was then purified by Mass Guided HPLC on an Agilent 1100 Purification unit to afford a white crystalline solid. Analytical LCMS: single peak (214 nm and ELSD) at 3.29 min (CH₃CN/H₂O/1%TFA, 4 min gradient). ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.36 (s, 1H), 8.19 (s, 1H), 8.12 (s, 1H), 7.86 (t, *J*=7 Hz, 1H), 7.46 (m, 3H), 2.9 (m, 2H), 2.44 (m, 2H), 1.11 (s, 9H) ppm. HRMS calc'd for C₁₅H₂₀BrN₃O₃S₂, 434.0202; found, 434.0183.

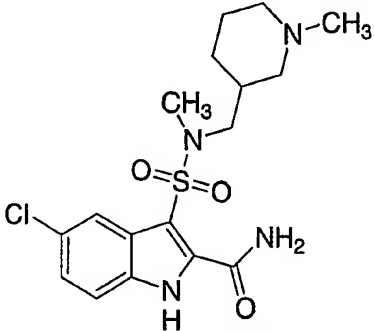
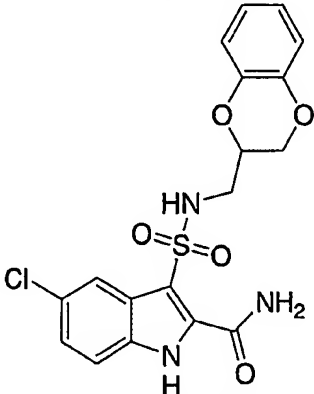
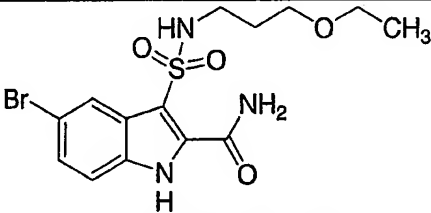
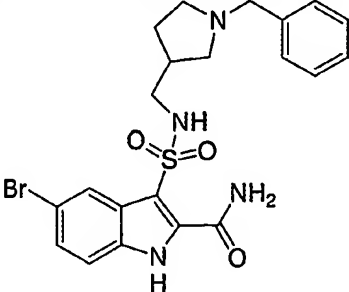
The compounds shown in the table below were also made using the above-described techniques.

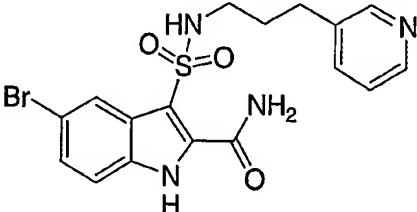
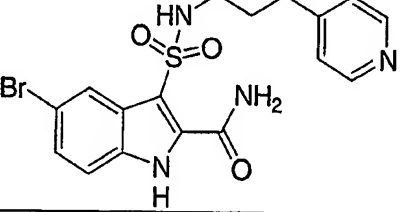
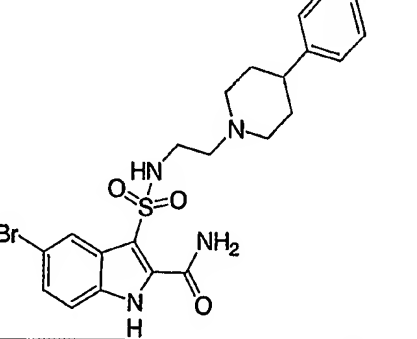
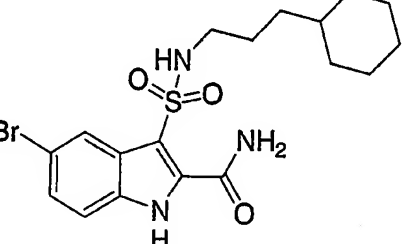
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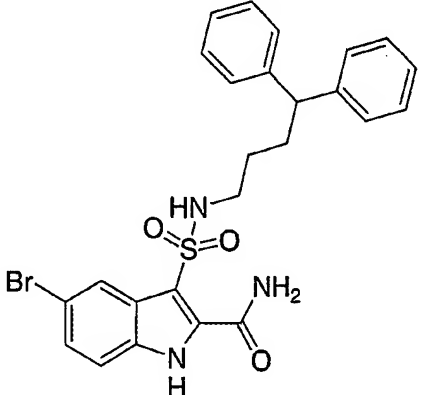
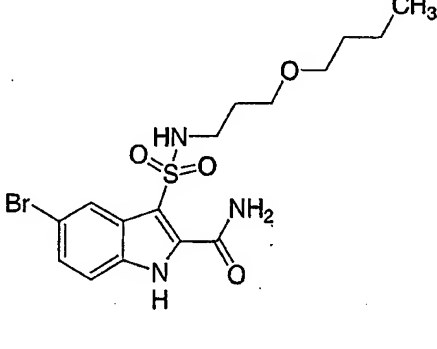
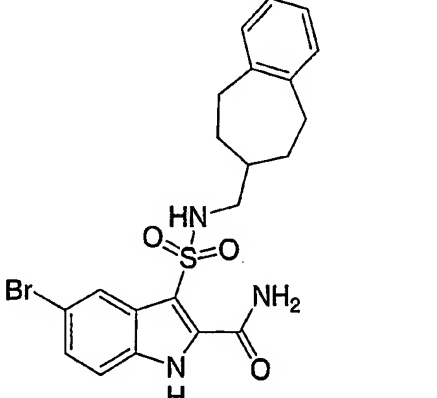
Name	Structure	ESI +MS
5-chloro-3- { [methyl(tetrahydro-2H-pyran-4-yl)amino]sulfonyl }-1H-indole-2-carboxamide		372
5-chloro-3-({[1-(2,3-dihydro-1,4-benzodioxin-2-yl)ethyl]amino}sulfonyl)-1H-indole-2-carboxamide		436
5-chloro-3-[(tetrahydro-2H-pyran-4-ylamino)sulfonyl]-1H-indole-2-carboxamide		358

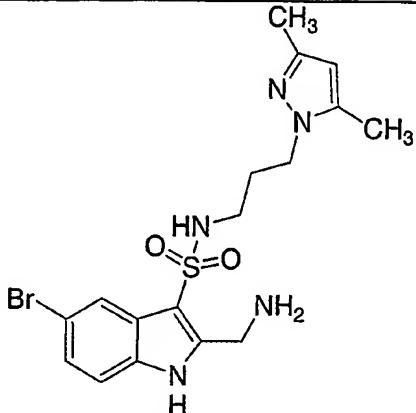
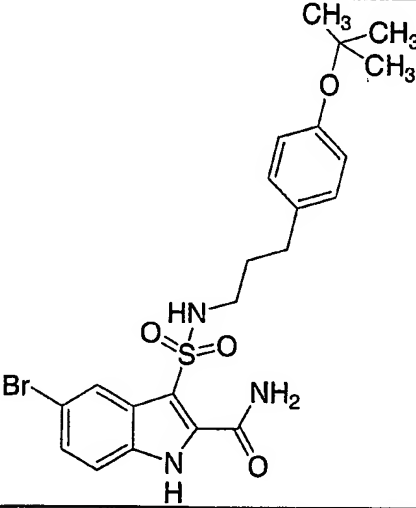
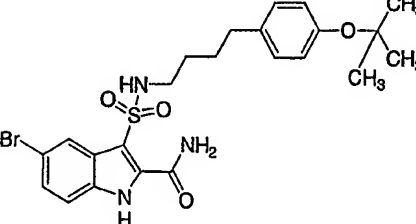
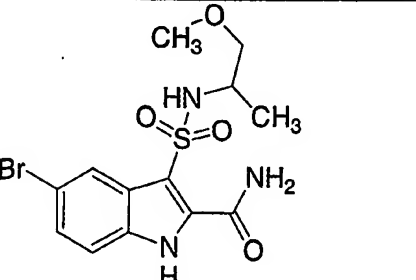
5-chloro-3-([(1,4-dioxan-2-ylmethyl)(methyl)amino]sulfonyl)-1H-indole-2-carboxamide		388
5-chloro-3-([(3-methyloxetan-3-yl)methyl]amino)sulfonyl)-1H-indole-2-carboxamide		358
5-chloro-3-[(tetrahydrofuran-3-ylamino)sulfonyl]-1H-indole-2-carboxamide		344
5-chloro-3-([(1,1-dioxidotetrahydrothien-3-yl)methyl]amino)sulfonyl)-1H-indole-2-carboxamide		406

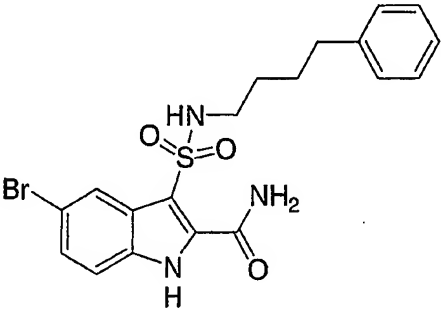
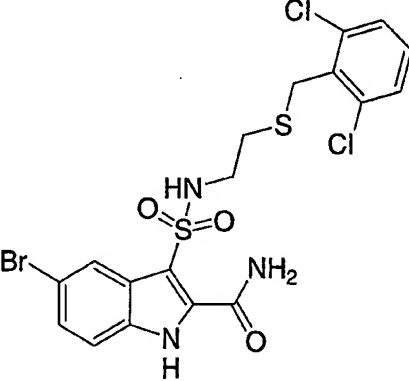
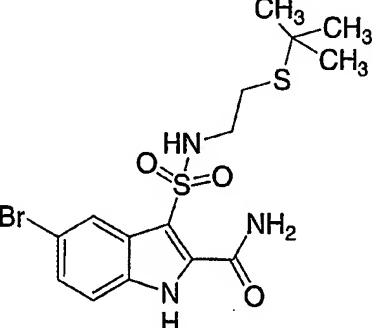
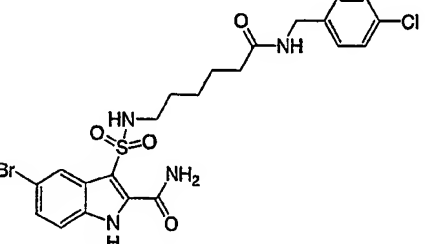
5-chloro-3-({[2-(3-phenyl-1 <i>H</i> -1,2,4-triazol-5-yl)ethyl]amino}sulfonyl)-1 <i>H</i> -indole-2-carboxamide		446
5-chloro-3-({[2-(2-methoxyphenyl)ethyl]amino}sulfonyl)-1 <i>H</i> -indole-2-carboxamide		408
5-chloro-3-({[3-(trifluoromethyl)benzyl]amino}sulfonyl)-1 <i>H</i> -indole-2-carboxamide		432
5-chloro-3-({[2-(2,3-dihydro-1 <i>H</i> -indol-1-yl)ethyl]amino}sulfonyl)-1 <i>H</i> -indole-2-carboxamide		419

5-chloro-3-({methyl[(1-methylpiperidin-3-yl)methyl]amino}sulfonyl)-1 <i>H</i> -indole-2-carboxamide		399.1
5-chloro-3-{[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino}sulfonyl}-1 <i>H</i> -indole-2-carboxamide		422
5-bromo-3-{[(3-ethoxypropyl)amino}sulfonyl]-1 <i>H</i> -indole-2-carboxamide		406
5-bromo-3-({[(1-benzylpyrrolidin-3-yl)methyl]amino}sulfonyl)-1 <i>H</i> -indole-2-carboxamide		393.1

5-bromo-3-{{(3-pyridin-3-ylpropyl)amino)sulfonyl}}-1 <i>H</i> -indole-2-carboxamide		439
5-bromo-3-{{(3-pyridin-4-ylpropyl)amino)sulfonyl}}-1 <i>H</i> -indole-2-carboxamide		437
1-[2-({[2-(aminocarbonyl)-5-bromo-1 <i>H</i> -indol-3-yl]sulfonyl}amino)ethyl]-4-phenylpiperidine		-07.1
5-bromo-3-{{(3-cyclohexylpropyl)amino)sulfonyl}}-1 <i>H</i> -indole-2-carboxamide		442

5-bromo-3-([(4,4-diphenylbutyl)amino]sulfonyl)-1H-indole-2-carboxamide		528.1
5-bromo-3-([(3-butoxypropyl)amino]sulfonyl)-1H-indole-2-carboxamide		434
5-bromo-3-([(6,7,8,9-tetrahydro-5H-benzo[a][7]annulen-7-ylmethyl)amino]sulfonyl)-1H-indole-2-carboxamide		478

5-bromo-3-({[3-(3,5-dimethyl-1H-pyrazol-1-yl)propyl]amino}sulfonyl)-1H-indole-2-carboxamide		456
5-bromo-3-({[3-(4-tert-butoxyphenyl)propyl]amino}sulfonyl)-1H-indole-2-carboxamide		561
5-bromo-3-({[4-(4-tert-butoxyphenyl)butyl]amino}sulfonyl)-1H-indole-2-carboxamide		546
5-bromo-3-({[(2-methoxy-1-methylethyl)amino]sulfonyl)-1H-indole-2-carboxamide		390

5-bromo-3-([(4-phenylbutyl)amino]sulfonyl)-1H-indole-2-carboxamide		450
5-bromo-3-([(2-[(2,6-dichlorobenzyl)thio]ethyl)amino]sulfonyl)-1H-indole-2-carboxamide		538
5-bromo-3-([(2-(tert-butylthio)ethyl)amino]sulfonyl)-1H-indole-2-carboxamide		458
5-bromo-3-([(6-[(4-chlorobenzyl)amino]-6-oxohexyl)amino]sulfonyl)-1H-indole-2-carboxamide		557

ASSAYS

The compounds of the instant invention described in the Examples above were tested by the assays described below and were found to have kinase inhibitory activity. In particular, the compounds of the instant invention inhibited IGF-1R or insulin receptor kinase activity with an IC₅₀ of less than or equal to about 100 μ M. Other assays are known in the literature and could be readily performed by those with skill in the art (see for example, Dhanabal *et al.*, *Cancer Res.* 59:189-197; Xin *et al.*, *J. Biol. Chem.* 274:9116-9121; Sheu *et al.*, *Anticancer Res.* 18:4435-4441; Ausprunk *et al.*, *Dev. Biol.* 38:237-248; Gimbrone *et al.*, *J. Natl. Cancer Inst.* 52:413-427; Nicosia *et al.*, *In Vitro* 18:538-549).

IGF-1R KINASE ASSAY

IGF-1R receptor kinase activity is measured by incorporation of phosphate into a peptide substrate containing a tyrosine residue. Phosphorylation of the peptide substrate is quantitated using anti-IGF-1R and anti-phosphotyrosine antibodies in an HTRF (Homogeneous Time Resolved Fluorescence) detection system. (Park, Y-W., et al. *Anal. Biochem.*, (1999) 269, 94-104)

MATERIALS

IGF-1R RECEPTOR KINASE DOMAIN

The intracellular kinase domain of human IGF-1R was cloned as a glutathione S-transferase fusion protein. IGF-1R β -subunit amino acid residues 930 to 1337 (numbering system as per Ullrich *et al.*, *EMBO J.* (1986) 5, 2503-2512) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen). Enzyme was purified by means of a glutathione sepharose column.

INSULIN RECEPTOR KINASE DOMAIN

The intracellular kinase domain of human insulin receptor was cloned as a glutathione S-transferase fusion protein. Insulin receptor β -subunit amino acid residues 941 to 1343 (numbering system as per Ullrich *et al.*, *Nature*, (1985) 313, 756-

- 761) were cloned into the baculovirus transfer vector pAcGHLT-A (BD-Pharmingen) such that the N-terminus of the IGF-1R residues are fused to the C-terminus of the GST domain encoded in the transfer vector pAcGHLT-A. Recombinant virus was generated and the fusion protein expressed in SF-9 insect cells (BD-Pharmingen)
- 5 Enzyme was purified by means of a glutathione sepharose column.

INSECT CELL LYSIS BUFFER

10mM Tris pH 7.5; 130mM NaCl; 2mM DTT; 1% Triton X-100; 10mM NaF;
10mM NaPi; 10mM NaPPi; 1X protease inhibitor cocktail (Pharmingen).

10

WASH BUFFER

Phosphate Buffered Saline (PBS): 137mM NaCl, 2.6mM KCl, 10mM Na₂HPO₄,
1.8mM KH₂PO₄, pH 7.4; 1mM DTT; 1X protease inhibitor cocktail

15 DIALYSIS BUFFER

20mM Tris pH 7.5; 1mM DTT; 200mM NaCl; 0.05% Triton X-100 and 50% glycerol

ENZYME DILUTION BUFFER

50mM Tris pH 7.5; 1mM DTT; 100mM NaCl; 10% glycerol; 1mg/ml BSA

20

ENZYME REACTION BUFFER

20mM Tris pH 7.4; 100mM NaCl; 1mg/ml BSA; 5mM MgCl₂; 2mM DTT

QUENCH BUFFER

- 25 125mM Tris pH 7.8; 75mM EDTA; 500mM KF; 0.125% Triton X-100; 1.25% BSA;
60 nM SA-XL665 (Packard); 300 pM europium cryptate labeled anti-phosphotyrosine
antibody (Eu-PY20)

PEPTIDE SUBSTRATE

- 30 Sequence LCB-EQEDPEPGDYFEWLE-NH₂; stock solution is 1mM dissolved
in DMSO; diluted to 1uM in 1X enzyme reaction buffer for 10X working stock.
(LCB = aminohexanoylbiotin)

ATP

Stock solution is 0.5 M ATP (Boehringer) pH 7.4; stock solution is diluted to 40mM ATP in enzyme reaction buffer to give 20X working stock solution

5 HEK-21 CELL LINE

Human embryonic kidney cells (HEK-293) (ATCC) were transfected with an expression plasmid containing the entire IGF-1R coding sequence. After antibiotic selection, colonies were screened for IGF-1R overexpression by western blot analysis. One clone, designated HEK-21 was selected for cell based IGF-1R

10 autophosphorylation assays.

HEK CELL GROWTH MEDIA

Dulbecco's Modified Eagle's Media (DMEM), 10% Fetal Calf Serum, 1X Penn/Strep, 1X Glutamine, 1X Non-essential amino acids (all from Life Technologies)

15

CELL LYSIS BUFFER

50mM Tris-HCl pH 7.4; 150mM NaCl; 1% Triton X-100 (Sigma); 1X Mammalian protease inhibitors (Sigma); 10mM NaF; 1mM NaVanadate

20 WESTERN BLOCKING BUFFER

20mM Tris-HCl pH 8.0; 150mM NaCl; 5% BSA (Sigma); 0.1% Tween 20 (Biorad)

METHODS25 A. PROTEIN PURIFICATIONS

Spodoptera frugiperda SF9 cells were transfected with recombinant virus encoding either the GST-IGF-1R β -subunit or GST-InsR fusion protein at an MOI of 4 virus particles/cell. Cells are grown for 48 hours at 27°C; harvested by centrifugation and washed once with PBS. The cell pellet is frozen at -70°C after the
30 final centrifugation. All subsequent purification steps are performed at 4°C. 10 grams of frozen cell paste is thawed in a 90ml volume of insect cell lysis buffer (BD-Pharmingen) and held on ice with occasional agitation for 20 minutes. The lysate is centrifuged at 12000g to remove cellular debris. Lysis supernatant was mixed with 45ml of glutathione agarose beads (BD-Pharmingen) and agitated slowly at 4°C for
35 one hour after which the beads were centrifuged and washed 3X with wash buffer.

The beads are resuspended in 45 ml of wash buffer and poured as a slurry into a chromatography column. The column is washed with 5 volumes of wash buffer and the GST-IGF-1R is eluted from the column with 5mM Glutathione in wash buffer. Pooled fractions are dialyzed vs. dialysis buffer and stored at -20°C.

5

B. IGF-1R KINASE ASSAY

The IGF-1R enzyme reaction is run in a 96 well plate format. The enzyme reaction consists of enzyme reaction buffer plus 0.1nM GST-IGF-1R, 100 nM peptide substrate and 2mM ATP in a final volume of 60 microliters. Inhibitor, in
10 DMSO, is added in a volume 1 microliter and preincubated for 10 minutes at 22°C. Final inhibitor concentration can range from 100uM to 1nM. The kinase reaction is initiated with 3 microliters of 40mM ATP. After 20 minutes at 22°C, the reaction is stopped with 40 microliters of quench buffer and allowed to equilibrate for 2 hours at 22°C. Relative fluorescent units are read on a Discovery plate reader (Packard).
15 IC50s for compounds are determined by 4 point sigmoidal curve fit.

C. INSULIN RECEPTOR KINASE ASSAY

The kinase reaction for insulin receptor is identical to that used to assay IGF-1R (above), except that GST-InsR is substituted at a final concentration of
20 0.1nM.

D. CELL BASED IGF-1R AUTOPHOSPHORYLATION ASSAY

IGF-1R inhibitor compounds are tested for their ability to block IGF-I induced IGF-1R autophosphorylation in a IGF-1R transfected human embryonic
25 kidney cell line (HEK-21). HEK-21 cells over-expressing the human IGF-1R receptor are cultured in 6-well plates (37°C in a 5% CO₂ atmosphere) in HEK cell growth media to 80% of confluence. Cells are serum starved for four hours in HEK growth media with 0.5% fetal calf serum. A 10X concentration of inhibitor in growth media is added to the cells in one-tenth the final media volume and allowed to
30 preincubate for one hour at 37°C. Inhibitor concentration can range from 10nM to 100uM. IGF-I (Sigma) is added to the serum starved cells to a final concentration of 30ng/ml. After a 10 minute incubation in the presence of IGF-I at 37°C, the media is removed, the cells washed once with PBS and 0.5mls of cold cell lysis buffer added. After 5 minutes incubation on ice, cells are scraped from the wells and lysis buffer
35 plus cells are transferred to a 1.5ml microfuge tube. The total lysate is held at 4°C for

twenty minutes and then centrifuged at top speed in a microfuge. The supernatant is removed and saved for analysis. Phosphorylation status of the receptor is assessed by Western blot. Lysates are electrophoresed on 8% denaturing Tris-Glycine polyacrylamide gels and the proteins transferred to nitrocellulose filters by electro-

5 blotting. The blots are blocked with blocking reagent for 10 minutes after which anti-phosphotyrosine antibody (4G10, Upstate Biotechnology) is added to a final dilution of 1:1500. Blots and primary antibody are incubated at 4°C overnight. After washing with PBS plus 0.2% Tween 20 (Biorad), an HRP conjugated anti-mouse secondary antibody (Jackson Labs) is added at a dilution of 1:15000 and incubated at

10 4°C for 2 hours. Blots are then washed with PBS-Tween and developed using ECL (Amersham) luminescent reagent. Phosphorylated IGF-1R on the blots is visualized by autoradiography or imaging using a Kodak Image Station 440. IC50s are determined through densitometric scanning or quantitation using the Kodak Digital Science software.

15